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VOLUME 3 *Mayo Clinic Number* NUMBER 3

THE MEDICAL CLINICS OF NORTH AMERICA

NOVEMBER, 1919

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CONTRIBUTORS TO THIS NUMBER

ARCHIBALD, A., M. D., Ch. B., Associate in Section on Medicine.[1] Fellow in Medicine.[2]

ASHBY, WINIFRED, B. S., M. S., Fellow in Immunology.[2]

BENEDICT, W. L., M. D., Head of Section of Ophthalmology in the Division of Surgery.[1] Professor o Ophthalmology.[2]

BERKMAN, D. M., B. S., M. D., Assistant in Section on Medicine.[1] Fellow in Medicine.

BISSELL, W. W., B. S., M. D., Head of Section on Pathology.[1] Assistant Professor of Pathology.[2]

BOOTHBY, W. M., A. B., A. M., M. D., Head of Section on Clinical Metabolism.[1] Assistant Professor of Medicine.[2]

BUMPUS, H. C., Ph. B., M. D., Assistant in Section on Urology.[1] Fellow in Urology.[2]

EUSTERMAN, G. B., M. D., Head of Section in Division of Medicine.[1] Assistant Professor of Medicine.[2]

GIFFIN, H. Z., B. S., M. D., Head of Section in Division of Medicine.[1] Associate Professor of Medicine.[2]

KENDALL, E. C., B. S., A. M., Ph. D., Head of Section on Biochemistry in Division of Pathology.[1] Associate Professor of Chemistry.[2]

LEMON, W. S., M. B. (Toronto), Head of Section in Division of Medicine.[1] Instructor of Medicine.[2]

MAGOUN, J. A. H. Jr., A. B., M. D., Fellow in Surgery.[2]

MARSH, H. E., Assistant in Section on Medicine.[1]

MUSSEY, R. D., M. D., Head of Section on Medicine.[1] Assistant Professor of Medicine.[2]

SANFORD, A. H., A. B., A. M., M. D., Head of Section on Clinical Laboratories, Division of Medicine.[1] Associate Professor of Clinical Bacteriology and Parasitology.[2]

STACY, LEDA J., M. D., Head of Section in Division of Medicine.[1] Instructor of Medicine.[2]

STOKES, J. H., A. B., M. D., Head of Section on Dermatology and Syphilology in Division of Medicine.[1] Assistant Professor of Medicine.[2]

SZLAPKA, T. L., B. S., M. D., Assistant in Section on Medicine.[1] Fellow in Medicine.[2]

VINSON, P. P., B. S., M. A., M. D., Assistant in Section in Division of Medicine.[1] Fellow in Medicine.[2]

WELD, E. H., B. A., M. D., Fellow in Surgery.[2]

WILLIUS, F. A., B. S., M. D., Associate in Section in Division of Medicine.[1] Fellow in Medicine.[2]

WOLTMAN, H. W., B. S., M. D., D. Sc. in Neurology, Associate in Section on Neurology in Division of Medicine.[1] Instructor in Medicine.[2]

---

[1] In the Mayo Clinic.

[2] On the Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota.

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REPORT OF A CASE OF RETINITIS CIRCINATA ASSOCIATED WITH TUBERCULOSIS

W. L. BENEDICT, M. D.

RETINITIS circinata is characterized by the appearance of a horseshoe-shaped zone of white deposits almost completely surrounding the macular region in which are irregular yellowish spots resting on a mottled, pale red background.

The areas of white exudate, unlike those found in nephritic retinitis, do not project into the macular region, but may extend beyond the wreath-like zone into the nasal side and into the periphery of the temporal side of the retina. Retinitis circinata is accompanied by reduction of visual acuity, alteration in the visual fields, and a subjective sensation of specks fixed in front of the eye. The onset of the disease is insidious, the progress slow, but it does not lead to complete blindness. It has been found in patients as young as twelve years, although the average age is fifty-four. It occurs more frequently in women than in men.[4]

The cause of this peculiar disease of the retina has not been determined definitely. Syphilis is often given as an etiologic factor, but apparently without other reason than that a few patients with retinitis circinata have also had syphilis. Other associated conditions mentioned are nephritis, arteriosclerosis, and leukemia. Atheroma and sclerosis of the retinal vessels have been described in retinitis circinata, and most of the changes found have been ascribed to these changes of the ves-

sels.[3] Tuberculosis has not been noted in a single case reported in the literature. The deposits in the retina have been thought to follow small hemorrhages or obstructions of invisible retinal arterioles. The disease is sometimes classified with massive hemorrhage of the retina.[5]

According to Fuchs, the spots consist of coagulated albuminous exudate similar to that found in albuminuric retinitis. Fuchs opposed the hypothesis that they are caused by arteriosclerosis or that they are degenerated blood-clots. deWecker believed the spots to be due to fatty degeneration of extravasated blood.[4]

In only one case, that of Ammenn,[3] has the retina been examined microscopically. This case seems to corroborate deWecker's theory. White fatty cells were found embedded in the internuclear layers of the retina, and the interspaces were filled with hyaline exudate and fibrin network containing fatty granular cells, as has been found in nephritic retinitis. There is a surprising agreement in the findings of Ammenn's case of retinitis circinata and in those of nephritic retinitis as regards the changes in the vessel walls and in the lumen of the choroidal vessels which lie near the most changed portions of the retina. Fatty granular cells were found in the lumen, and spaces in the walls of the vessels were filled with blood and glistening bodies resembling crystals, the corners of which stained black with osmic acid. The supporting tissue of the retina in Ammenn's case showed changes characteristic of senile degeneration.

It seems probable that the cause of the deposits in the retina lies in changes in the vessel wall. While the changes which occur in the retinal layers during the formation and deposit of the white substance may be accompanied by small hemorrhages, there is insufficient evidence to warrant the belief that hemorrhage always precedes the formation of the white substance.

The form of the zone of deposit may change, due to absorption of some areas of exudate and the formation of others, without visible hemorrhage appearing at any time. The patches of exudate, resembling fluffy cotton wool, seen in acute nephritic retinitis are not present. The white dots with irregular borders become confluent, but the edges of the borders are always

sharply defined, and are not surrounded by areas of hemorrhage or edema. The edema of the retina is confined to the inside of the zone of exudate.[1] On the edematous background of mottled red are small yellowish areas quite different from the background of nephritic retinitis or the retinitis of arteriosclerosis; they are peculiarly significant in differentiating true retinitis circinata and retinitis from other causes which may resemble it in the general distribution of exudate. That the changes are not entirely due to sclerosis of the retinal vessels is believed from the fact that a few typical cases have been found in persons too young to be suspected of having sclerosed arteries. It is more probable that metabolic disturbances are responsible for both the vascular changes and the deposit of fat in the retina. In Blake's case the exudate was preceded by a massive hemorrhage, but the patient had also high blood-pressure (200 mm.) and was reported to have had chronic interstitial nephritis.

The case which I shall now report is unique because the associated physical findings differ from those in any case previously described.

Mr. G. W. F., Case 286629, aged seventy-four, came to the clinic August 26, 1919, complaining of failing vision and difficulty in hearing. The patient's mother and one sister died of tuberculosis and his one brother is dead, cause unknown. One sister is living and in poor health. There is no history of cancer, Bright's disease, or disease of the nervous system in the family. The past three winters the patient has spent at a resort because of ill health; eight weeks of the past year he was in a hospital. After leaving the hospital he noticed that his vision, which had been failing for about one year, was markedly diminished. He had no pain or inflammation in either eye. His vision continued to fail rapidly. In March, 1919, he developed a sudden severe stabbing pain in the right ear. He returned to the hospital, where he was treated by hydrotherapy. Hot packs were kept on his head. He became very dizzy, his head dropped backward, and he was obliged to sit or lie to keep from falling. He did not vomit or have severe headaches. He has had no night-sweats or cardiac symptoms. His appetite has been good and

he has had no genito-urinary trouble. All his teeth have been removed. The systolic blood-pressure was 120, the diastolic was 60; pulse was 100, and temperature was 99.8° F. at 8 o'clock in the morning. The heart-beats were rapid; the first sound at the tricuspid area was accentuated; there was no murmer. The entire right lung had many râles, moist and dry. *x*-Ray examination showed tuberculosis with cavitation of the upper right lung.

Ophthalmoscopic examination of the left eye showed the media to be clear. The nerve head was round and reddish brown with somewhat hazy margins. A slight edema of the retina, beginning at the nerve head and extending outward in all directions, was more marked in the temporal side of the disk, greatest in the macular region, and thinned out toward the periphery. A large zone of white exudate in the retina, beginning near the disk and extending around the macular region, ended near the disk so as to form a wreath-like figure. This zone was from about one-half to one disk's diameter in width, the widest part being furthest removed from the disk. The central portion of the area thus enclosed showed a grayish hue, over which were scattered several small yellowish spots. There was no evidence of hemorrhage in any part of the fundus. The white spots appeared to be raised rather than depressed. There were no changes in the pigment. A few areas of similar deposit were scattered in the nasal side of the retina without regular form of distribution. The arteries were not contracted. There was no arteriovenous compression or other signs of arteriosclerosis. The central portion of the fundus gave the general impression of degeneration of the retina (Fig. 97).

The right eye showed changes similar to those found in the left, but without any attempt at wreath formation. The white spots were scattered about both parts of the fundus, as numerous on the nasal side as on the temporal side. The macular region in the right eye did not show the central degeneration. There was no edema or yellow spots.

The etiology of the retinitis circinata in this case is quite obscure. The general examination showed no evidence of sys-

Fig. 97.—Case 286689. Retinitis circinata associated with pulmonary tuberculosis in a man aged sixty-two.

temic or cerebral sclerosis. At no time has the patient had any evidence of nephritis. The sclerosis of the retinal vessels was no more marked than might be expected in a man of this patient's age.

Syphilis was excluded through biologic tests. Examination of the blood gave no clue. It is quite probable that the retinitis in this case is due to metabolic disturbances secondary to pulmonary tuberculosis. Retinitis circinata may not be so rare as has been supposed, and if searched for it might be found more often in persons with marked emaciation from infectious disease or in old age.

BIBLIOGRAPHY

1. Blake, E. M.: The Etiology of Retinitis Circinata, Trans. Amer. Ophthal. Soc., xiv, 753–762, 1915, 1916.
2. Collins, E. T., and Mayou, M. S.: Pathology and Bacteriology, System of Ophthalmic Practice, edited by Pyle, W. L., Philadelphia, Blakiston, 191, 192, 1911.
3. Fuchs, E.: Retinitis Circinata, Arch. f. Ophthal., xxxix, 229–279, 1893.
4. Graefe-Saemisch Handbuch: Krankheiten der Netzhaut, vii, A 2, Leipzig, Engelmann, 1261–1265, 1916.
5. Parsons, J. H.: The Pathology of the Eye, New York, Putnam, ii, 600–602, 1905.

FACIAL PARALYSIS

H. W. WOLTMAN, M. D.

THE facial nerve is perhaps more frequently paralyzed than any other one nerve. Alterations in the activity and behavior of muscles in its domain yield more information, by reason of intimate anatomic and physiologic relations with the rest of the central nervous and muscular systems, than is afforded by the muscles in any other portion of the body. Delicate variations in the muscle tonus betray the psychic and emotional status in a manner so subtle that we vaguely attribute its interpretation to the process of intuition. The flabby, vacant, and quivering facies of the general paretic, the mask-like countenance of the victim of paralysis agitans, betray the diagnosis at a glance.

Facial paralysis proper, or prosopoplegia, may be infranuclear, nuclear, or supranuclear, depending on the seat of the lesion. Clinically, these separate types are fairly well characterized, as the following cases will illustrate:

CASE I (A263454).—Miss J. H., aged seventeen, came to clinic complaining of paralysis of the right side of the face dating from an injury which she sustained one year before when an automobile in which she was riding overturned. She was immediately rendered unconscious and remained so for one week. At the time of the injury bleeding from the right ear was profuse. On recovering consciousness the patient was troubled with a diplopia which disappeared in the course of a few days. She has since been quite unable to move the right side of the face, and has been totally deaf in the right ear.

Examination disclosed a very striking asymmetry of the face, the right side appearing swollen and hanging somewhat lower than the left side; this was particularly marked over the

cheek. The right eyebrow was a trifle lower than the left and the normal curve was partly obliterated. The nasolabial fold on the right was not so deep as its fellow on the left and the angle of the mouth on the paralyzed side was moderately depressed. The slight normal wrinkling of the skin was absent on the right, particularly over the brow; this was especially evident near the midline. On being asked to raise the eyebrows, the patient said she was unable to do so; however, on being requested to look at the ceiling, it was noticed that the left side wrinkled normally, while the right side did not move. When the eyes were closed forcibly the left closed in the normal manner, while the right closed only slightly, and the eyeball could be seen to turn upward and outward, leaving the sclera partly exposed, producing what is known as Bell's phenomenon. The same condition, the mother said, was present during sleep. On attempting to show her teeth, only the left side of her mouth responded. She had difficulty in eating, the food accumulating in the right cheek, and often she found it necessary to insert her finger to bring the food back between the teeth; in drinking, the fluid frequently escaped between her lips on the right. She was unable to pucker her lips on the paralyzed side, and could not whistle or blow out a flame, as the lips puffed out, permitting the air to escape through a large opening. The ala nasæ on the left rose slightly with each inspiration; on the right this movement was not only missing but also the ala was drawn inward, partially obstructing respiration. The patient was able to taste salt, sugar, tartaric acid, and quinin on the left side of her tongue, but she could not taste them when they were placed on the right side. Hearing, tested by noises and tuning-forks, revealed complete deafness on the right. Examination of the membrana tympani on the right showed much scarring and thickness. A Bárány test gave evidence of a definite lesion of the right cerebellopontile angle. The palate, on phonation, was seen to move vertically upward. The protruded tongue deviated to the left; when the paralyzed angle of the mouth was raised, however, it was seen to project straight forward. Whenever the patient was exposed to wind, she had noted a tendency for

tears to run down the cheek on the right; this was probably due to the slight ectropion of the lower lid, preventing perfect approximation of the punctum lacrimalium to the globe of the eye.

Discussion.—In this case the paralysis of the facial nerve is due to a fracture of the base of the skull, the nerve being injured at the intratemporal portion, where it is accompanied by the chorda tympani and the auditory nerve. The prognosis as to recovery is not very good. In all probability it will be necessary to consider an anastomosis of the spinal accessory or hypoglossal nerve to the facial nerve. Should this prove successful, the patient would not only be enabled to move the paralyzed side somewhat, but also a more normal tonicity would be restored, making the features more symmetric.

The following case illustrates the more common type of Bell's palsy in which the etiologic factor was exposure with probably some added infection.

CASE II (A262918).—Mr. W. R., farmer, aged thirty, presented himself for examination with paralysis of the left side of the face. Excessive use of alcohol and venereal disease were denied. The patient's farm is located in Saskatchewan, where the wind is often very high, particularly in the month of February, at which time the present trouble began. This he attributes to an accident he had while working on the bottom of a well, when a bucket dropped on his head; he was not rendered unconscious, and on the whole appeared to suffer no ill effects from the accident. The following day he worked on the surface, but removed a wind break which had been put up for protection. That evening severe pain, dull and aching with an occasional acute twinge, developed behind his left ear. He was unable to close his left eye properly, and somewhat later found that his lips did not move as they should.

Examination showed a complete paralysis of all the muscles supplied by the left facial nerve. Sensation of taste, as tested for salt, sour, sweet, and bitter, was found to be slightly less on the left side than on the right side of the tongue. On phonation, the soft palate deviated slightly toward the left. An electric

examination gave values as follows: Complete absence of response to faradic stimulation of the facial muscles on the left. Tested with the galvanic current these muscles gave decidedly slow responses; the cathodal closing contraction could be obtained with 1.2 ma., the anodal closing contraction with 0.3, and the anodal opening contraction with 1.8. The rest of the examination was practically negative, except that the tonsils were very septic.

CASE III (A249850).—Mr. T. W., aged thirty, master mechanic, came to the clinic complaining of paralysis of the left side of the face. The first symptoms appeared fifteen days before, when the patient noted an inability to close the left eye and a drooling of saliva on speaking. He tried to whistle, but found this impossible, and had considerable difficulty on attempting to pronounce certain words, particularly those containing labials. The only etiologic factor that could be discovered in the case was tonsillitis, which the patient had had intermittently, and which was present at the time of the onset of the paralysis. On the second day the left side of his tongue became very painful and entirely covered with white blisters, the size of a pin-head; the right side appeared normal. Gradual improvement followed the application of alum. There was tenderness over the left side of the face at the time. Certain sounds, for instance, a shrill whistle, caused a sharp pain in the left ear; this symptom had been present only since the onset of the paralysis.

On examination a very marked horizontal and rotary nystagmus appeared when the patient was requested to look toward the right or toward the left. The entire left side of the face, including the forehead, was completely paralyzed. He was unable to distinguish the difference between salt, sugar, tartaric acid, and quinin on the left side of the tongue, but could do so readily on the right side. The Bárány test showed a lesion on the left side involving the brain stem. No response could be obtained to the faradic current; responses to the galvanic current were very small and sluggish. A spinal puncture was made,

the fluid giving a negative Wassermann, a negative Nonne, and 5 small lymphocytes for each cubic millimeter.

Discussion.—This patient illustrates a somewhat unusual type of Bell's palsy, in that it was accompanied by an herpetic eruption over the portion of the tongue supplied by the chorda tympani, and that a definite hyperacusis, dependent on a paralysis of the nerve supplying the stapedius, was present. In looking for the possible etiology it was found that the patient had a leukocyte count of 10,800 and that the tonsils were moderately enlarged and contained some pus, and that two of the teeth showed very definite evidence of apical infection on *x*-ray examination. On the strength of this the patient was advised to have his tonsils removed and the infected teeth extracted.

CASE IV (A262035).—Mr. N. P., aged forty-three, an ore miner, came to the clinic because of paralysis of the right side of the face. The patient's habits were good and he denied venereal infection. Three years before, after he had slept with a strong wind blowing over the right side of his face, he awakened with severe pain over the right side of the face and the upper portion of the neck, which continued for sixteen hours and then disappeared. He had trouble in chewing, as the food would accumulate in the right buccal cavity, making it necessary to press on the cheek to force the food back between the teeth. A "heavy" sensation persisted on the right side of the face. He was unable to close the right eye, could not whistle, and on laughing the face drew toward the left. After about one month he was able to close the eye somewhat. Some months subsequently a new difficulty arose: when he chewed his food the right eye winked with every movement of the mouth. This became most embarrassing.

On examination it was found that the forehead could not be wrinkled quite so much on the right as on the left. The eyelids, when closed, covered the globes almost completely, save on the right, where a small slit remained; when the lids were closed as tightly as possible, the one on the right could be more readily

forced open than its fellow. The left angle of the mouth moved considerably more than the right when the patient smiled. He could pucker his lips, but on drawing them firmly over the examiner's fingers the right side gave way easily as compared with the left. Whenever the patient chewed or moved his lips the right eye closed simultaneously. In winking the right eye the corresponding angle of the mouth moved as if smiling, and a number of the platysmal fibers stood forward strikingly. The electric reactions were fairly normal. The teeth showed a marked pyorrhea.

Discussion.—This case is of interest as it illustrates the faulty regeneration of nerve-fibers which often takes place, although rarely to such a marked degree as in this case. It seems that fibers that should have grown to the muscles moving the angle of the mouth have grown through the upper facial branch to supply muscles about the eye, and that fibers intended for the orbicularis oculi have grown to supply those of the mouth and platysma myoides. This phenomenon is so common in cases of facial paralysis in which partial regeneration has occurred that it not infrequently reveals an old paralysis which the patient may have quite forgotten. In the majority of cases of this kind only a slight simultaneous "winking" of the cheek or upper lip appears every time the eyes are closed. It was also noted in this case that at times the face appeared to be drawn toward the paralyzed side. This has been explained by assuming that the nucleus of the facial nerve becomes hyperirritable under these conditions, causing an undue amount of contraction of the originally paralyzed fibers. Spiller has recently ventured another explanation, which seems to represent more nearly what actually occurs, namely, that the frequent, excessive, and unnecessary movements which take place about the face, due to faulty regeneration, bring about a general overaction of these muscle-fibers with resulting hypertrophy and contracture.

CASE V (A262998).—Mrs. P. W., aged seventy-one, presented herself for examination because of facial paralysis on the left side. She had not noticed this until someone informed her

that she moved the right side of her face only. The patient very much feared that she had had a stroke of paralysis, although she had not become unconscious and had not been dizzy.

Examination in this case showed complete paralysis of the right side of the face. The patient's attention was poor, there was some diminution of joint sensibility in the toes, vibration sensibility was somewhat impaired over the lower extremities, and other characteristics of a cerebrospinal arteriosclerosis were evident. The paralyzed muscles did not respond to the faradic current, and responses to the galvanic current were definitely sluggish as compared with those on the right. Cathodal closing contraction was obtained with 1.2 ma., anodal closing contraction with 0.3 ma., and anodal opening contraction with 3.2 ma.

Discussion.—On account of the associated arteriosclerosis and the high blood-pressure in this old lady it was necessary to determine whether the paralysis was actually due to a cerebral lesion or whether it was the less serious Bell's palsy. The fact that the upper branch of the seventh nerve was paralyzed to the same extent as the others, and that the electric responses showed evidence of degeneration, placed the diagnosis of Bell's palsy beyond question.

The following case is instructive in that it teaches us the significance of a slowly progressing paralysis of the facial nerve.

CASE VI (A202978).—Mr. D. P., aged twenty-seven, a farm hand, came to the clinic complaining of noises in his head and pain in the right ear. One year before the patient had noticed in attempting to whistle that the air escaped through the right side of his mouth without sound. He paid no attention to this, but a week later was greatly troubled with an excessive flow of tears over the right cheek. The lacrimal duct was dilated several times in succession without relief. About six months later he had successive attacks of severe pain, of twenty minutes' duration, in the region of the right external auditory meatus. The following month he noted stiffness in the right side of the face, defective speech, and a progressive

weakness of the muscles. His tonsils were removed, but without relief. He was then seen by an otologist, who, on examination of the auditory canal, found a swelling which he incised. No pus was obtained, but hemorrhage was profuse.

Examination showed a complete paralysis of all of the branches of the facial nerve on the right. There was some diminution but not complete absence of taste sensibility on the corresponding side of the tongue. Examination of the auditory canal showed a small, soft, red, non-pulsating tumor on the posterior wall near the membrana tympani. The patient complained of buzzing in the ear, which was very annoying and which was not relieved by pressure over the carotid. Hearing was also greatly impaired on this side. *x*-Ray examination showed a cavity formation in the right mastoid region. A tentative diagnosis of hemangioma was made.

Discussion.—The most frequent etiologic factor of facial paralysis is ordinarily given as rheumatic or refrigerative, since it usually follows exposure to drafts, as in sleeping near an open window, riding in a train or automobile, following a shampoo, and so forth. Infection is probably contributory in many cases. The individual factor is often striking; it may be that congenital anomalies, such as an abnormally small fallopian canal, play a part. Not infrequently the cause is to be found in otitis media and mastoiditis, particularly tuberculous. Among the other causes are tonsillitis, parotitis, erysipelas, articular rheumatism, herpes, puerperium, diphtheria, leprosy, gout, diabetes mellitus, leukemia, and syphilis. The paralysis of the facial nerve sometimes seen in the course of antisyphilitic treatment, particularly after the administration of salvarsan or allied preparations, is probably to be regarded in the light of a Herxheimer reaction. Injuries about the ear, notably basal fractures, blows, gunshot wounds, surgery in the region of the mastoid and about the parotid, alcohol injections for trifacial neuralgia and other pain about the face, pressure from obstetric forceps, and pressure on the nerve during sleep have all been noted as causes.

Facial paralysis occurs frequently as a symptom of meningitis. Sometimes the facial nerve is involved with other nerves

in the course of a multiple neuritis. Occasionally the paralysis is congenital, as illustrated by Case X. In the most common type of peripheral facial paralysis, or Bell's palsy, which constitutes about 73 per cent. of these cases, certain prodromal symptoms not infrequently occur. The patient may be recovering from a cold when he experiences a rather mild, aching, diffuse pain and tenderness in and about the region of the corresponding external auditory meatus. This may disappear or continue until the onset of the paralysis, which comes on with rather characteristic suddenness. A slowly progressive development is decidedly rare. The patient may discover the condition in the morning when washing his face, brushing his teeth, shaving, looking in the mirror, or on finding some difficulty in eating or drinking; frequently he knows nothing of it until it is accidently discovered by some member of the family. A slight local swelling may be present. Not infrequently ringing and buzzing in the ear, vertigo, which may be very violent, fever, and feeling of general malaise are noted, particularly in instances in which infection is prominent. Paresthesias of taste have also been noted; there may be complaint of a metallic taste, and often the information is volunteered that the sense of taste has been impaired.

The essential objective features of a peripheral facial paralysis have been sufficiently emphasized in the reports of cases. Diminution in acuity of the sense of smell, occasionally noted on the side paralyzed, can usually be accounted for by the failure of the ala nasæ to rise on inspiration; in fact, the current of air passing into the nostril usually brings about approximations of the ala to the nasal septum, causing partial obstruction. While some writers attribute a partial innervation of the palate to the facial nerve, this is probably not correct; asymmetry of movement, as sometimes noted, is probably an accidental and unrelated finding or may be explained by simultaneous involvement of other cranial nerves. The same may be said of deviation of the tongue; this is often noted, but is usually deceptive, as it disappears when the drooping angle of the mouth is retracted by the examiner's finger.

Paralysis of the stylohyoid and posterior belly of the digastric muscles may produce no striking objective change, although the floor of the mouth may appear somewhat depressed on the corresponding side. Paralysis of the extrinsic muscles of the ear usually cannot be discovered clinically save by the use of the electric current. In case the nerve to the stapedius muscle is involved, hyperacusis or oxyokeia may be noted, especially for deep tones, as the protective action of this muscle is destroyed. The symptom is usually absent and, when it does occur, is noted early in the course of the paralysis.

Vasomotor changes are not mentioned and do not become manifest clinically. Diminution in lacrimal secretion on the corresponding side is said to occur and may be demonstrated by inserting pieces of filter-paper in the palpebral fissures near the median canthus of each eye and then irritating the mucous membrane of the nose with a probe. It is often noted that tears run down the paralyzed side of the face, due to the ectropion of the lower lid that results. Diminution in the flow of saliva can sometimes be noted by simply observing the orifices of the ducts of the submaxillary and sublingual glands, while the patient takes a whiff of strong acetic acid. Perspiration may be diminished or increased on the side of the paralysis; it is recalled in this connection that sudoral fibers from the cervical sympthetic also supply the face.

Disturbances of taste due to involvement of the chorda tympani, supplying the anterior two-thirds of the tongue, are relatively common. Usually the loss of taste is not complete. Herpes of the tongue rarely accompanies or precedes a facial paralysis, as in Case III. It may also be present in and about the external auditory canal. Hunt has described a syndrome of facial paralysis, deafness, otalgia, and herpes oticus which he attributes to an inflammatory process of the geniculate ganglion, analogous to the zoster caused by irritative lesions of the posterior spinal root ganglia. The great and the small superficial petrosal nerves connecting the facial nerve with the sphenopalatine and the otic ganglia may be looked on as providing a reflex path between the seventh and the fifth nerves (Fig. 98).

It is advisable to determine as nearly as possible the exact point of injury in the course of the nerve. Figure 98 indicates how the anatomic relations of the nerve often permit of this localization, although it may be rendered difficult by reason of the fact that the entire cross-section is not always involved.

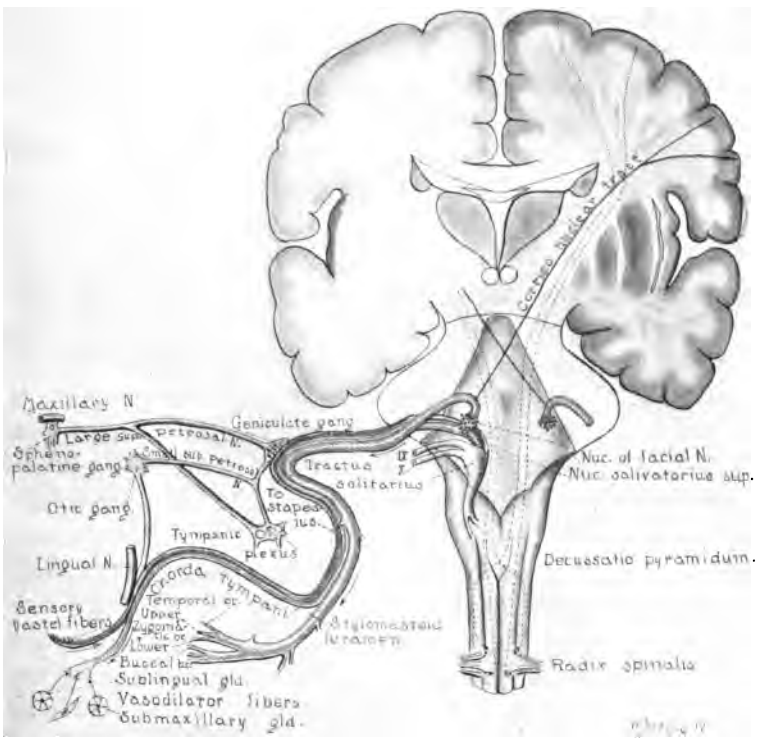


Fig. 98.—Diagram of facial nerve and its connections, based on the most recent and now generally accepted view.

The electric reactions are often of much diagnostic and prognostic value. It is well to remember that even with a complete and permanent paralysis these reactions sometimes remain normal. Nuclear and supranuclear paralysis may be exemplified by the succeeding cases:

The value that a facial paralysis may have in localization of lesions of the brain stem is illustrated by Case VII.

CASE VII (A241601).—Mr. J. M., aged twenty-three, railway section hand, was brought to the hospital in a stuporous condition, complaining of headache and weakness. The patient had been practically well until two months before, when a headache gradually appeared. This became progressively more intense, and was almost continuous. It was always most marked in the frontal region, and was bilateral. As the pain increased in severity, it radiated to the occipital region and to some extent to the left ear. The headache was greatly aggravated by any sudden turn of the head or jar of the body. Occasionally a marked tinnitus, particularly on the right side, and sometimes a very intense vertigo appeared. During the month preceding the examination the patient developed characteristic projectile vomiting. The findings which had a definite bearing on these complaints were as follows: Fluctuation of the pulse-rate between 46 and 94 beats for each minute. The fundi oculi were negative, save for a slight hyperemia of the left nerve head. *x*-Ray of the head was negative. If the patient looked toward the right, a marked horizontal nystagmus appeared; this was also present, but less in degree, if he looked toward the left. The external rectus on the right was slightly deficient in power, while that on the left was completely paralyzed. The pupils were moderately dilated and their reaction to light was somewhat sluggish. There was a definite weakness of all muscles, including the frontalis, supplied by the left facial nerve; the muscles on the right were not affected. There seemed to be some weakness of the right trapezius as well as a very definite motor impairment of all muscles on the right of the body. Speed of movement was also definitely reduced on the right as compared with that on the left. Sensibility to pain was probably somewhat diminished on the right side of the face, but sensation was otherwise practically normal; a satisfactory examination in this respect could not be made, however, on account of the patient's clouded mentality. Attention and cooperation were very poor. The tendon reflexes of the arms were equal on both sides, but slightly more active than normal. The patellar reflex was very much increased on the right and mod-

erately so on the left. The tendo achillis reflex was very active on the right and absent on the left. The corneal reflexes were diminished on both sides, but more so on the right than on the left. The pharyngeal reflex was almost absent. The cremasteric reflexes were moderately diminished. The plantar response was normal on the left; on the right it was extensor by the methods of Babinski, Oppenheim, and Chaddock. There was slight ataxia of the left arm and a somewhat more marked ataxia of the right. On being asked to pronate and supinate the hands rapidly, bilateral adiodokokinesis, or a failure of proper muscular co-ordination, was marked. Both legs showed definite ataxia, which was very marked on the right. The patient had difficulty in standing with his feet placed closely together; this was equally difficult with the eyes open as with them closed, and hence could not be interpreted as a true Romberg symptom.

A static tremor was present on both sides, but there was no movement tremor.

Discussion.—A diagnosis of tumor of the pons involving the left sixth and seventh nerves and the left pyramidal tract above its decussation was made. This represents one type of so-called paralysis alternans which is characteristic of pontine lesions. The paralysis of the external rectus on the left, in this case, is probably due also to a direct encroachment of the tumor on this nerve, although it may be stated that in general an abducens paralysis in patients exhibiting a marked intracranial pressure is of no definite localizing value, as the nerve is so easily paralyzed by pressure alone. The patient developed a general convulsion the afternoon of his admission to the hospital and died shortly afterward. Necropsy revealed a glioma of the pons, the infiltration being more marked on the left than on the right.

The tumor was very soft and showed definite evidence of recent hemorrhage.

The following case differs from the preceding ones in that the paralysis was due to an involvement of the upper motor neurone of the seventh nerve.

CASE VIII (A286343).—Mr. W. D., aged fifty-six, a brakeman, came to the clinic complaining of headaches, dizziness, weakness, nausea, and vomiting. The patient had been entirely well until he had an attack of facial erysipelas. As soon as this disappeared, he developed headaches which were principally frontal and produced the sensation of pushing his eyes out. The headache varied considerably in intensity, although he was never entirely free from it. He began to feel tired and could fall asleep at almost any time; he lacked ambition and could be made to work only by constant urging on the part of his wife. On Christmas day, 1918, when he felt particularly weak and tired, he suddenly became very weak and dizzy while walking along the street. He leaned up against a building to steady himself and then continued walking. He remembers nothing of his further activities, however, until about an hour later, when he found himself in the station house, where he was told that he had been picked up unconscious and considerably bruised and scratched. Difficulty in walking gradually developed. His left leg felt "dead," and rubbing it afforded no relief. For about two months he had noticed some trouble with his left hand. This was especially marked when he attempted to button his shirt or put on his collar. He became greatly irritated at these times, tearing up the collar, and finally appealing to his wife for help. His sight began to bother him about six months before; he changed glasses, but continued to get worse, and finally gave up reading entirely. During this time he occasionally vomited with striking suddenness, making it impossible for him to reach a vessel in time.

The story, on the whole, is one of progressing weakness and ataxia of the left arm and leg. Examination of the fundus showed a condition more like that of a toxic neuroretinitis with exudate than that due to intracranial pressure. The patient was unable to see objects on the left. This defect in vision was present in both eyes, constituting a left homonymous hemianopsia. There was a questionable nystagmus on looking toward the right or left. The left pupil was a trifle larger than the right. The masticatory muscles were possibly a trifle weak on

the left as compared with those on the right. On being asked to wrinkle his forehead, the patient did so very easily; no asymmetry was noted. On closing his eyes tightly and on moving the muscles about his mouth a very definite paresis on the left was evident. The muscles of the left arm and leg were much weaker than those of the right, and the speed of the movements was correspondingly diminished. The patient, while able to move his left arm with normal amplitude, was quite unable to touch his nose or to recognize objects placed in his left hand when his eyes were closed. He had the same difficulty, although somewhat less marked, in moving his left leg. Movements in the right arm and leg were normal. Sensation for touch and temperature was markedly diminished over the entire left half of the body, including the face. Vibration and joint sensibility were likewise impaired on the left. The biceps, triceps, and supinator reflexes were somewhat more active than normal on the left and considerably diminished on the right; the left patellar and Achilles' reflexes were more active than the right; the abdominal reflexes could not be obtained definitely. The corneal reflex appeared to be slightly diminished on the left as compared with that on the right. On testing for the Babinski phenomenon, the right plantar was constantly flexor, while the left occasionally showed a slight extensor response. The patient's mental reactions were very sluggish and his attention poor.

Discussion.—A diagnosis of a tumor of the brain, probably subcortical and involving the right internal capsule at its posterior portion, was made. This was verified by operation, when a glioma was found.

The case of bilateral supranuclear facial paralysis is of considerable interest:

CASE IX (A264731).—The patient, Mr. O. K. M., aged fifty-five, a Norwegian farmer, came to the clinic complaining of difficulty in talking. A full history could not be obtained because of his imperfect speech and foreign language. For about eight years he had not been able to speak clearly or swallow easily; the trouble began gradually and grew progres-

sively worse. The patient's sister, aged fifty-seven, had had the same condition for the past ten years.

An examination of the eyes, including the fundus, revealed nothing of significance. When the patient attempted to carry out voluntary movements on command, such as closing his eyes, showing his teeth, whistling or putting out his tongue, he did it very poorly. He had great difficulty in trying to swallow;

Fig. 99.—Case IX (A264731). The mask-like countenance of a patient with a bilateral upper motor neurone lesion.

when the substance was finally started, it went down easily. The face, however, which was decidedly mask-like (Fig. 99), moved very well with all emotional movements. The patient smiled easily and with a normal or even excessive amplitude of movement; he cried with overaction of the facial muscles and winked his eyes normally. His speech was of the pseudobulbar type and exceedingly slow. There was no atrophy of the muscles about the mouth or tongue. Voluntary movements of the tongue

were very slow, and this slowness was also characteristic of other movements which the patient attempted; his arms and legs appeared to be quite rigid. In walking there was marked shuffling and some propulsion. The patellar reflexes were slightly more active than normal; the abdominal reflexes were obtained with difficulty. The plantar response and other tendon reflexes were normal. Sensation appeared normal, as was also sphincteric control.

Discussion.—This case strongly suggests a pseudobulbar palsy which, indeed, it might be called. A familial element was present, however, which probably means that the case is one of the familial degenerations occasionally seen in the nervous system, which cannot always be classified definitely. Emotional and reflex movements were not only present but also were greatly exaggerated, while voluntary movements were carried on only with the greatest difficulty.

Case X illustrates a congenital defect of the seventh nerve.

CASE X (A270472).—W. B., a girl aged thirteen, came for examination because of an absolutely mask-like and fixed expression in her face which had been present since birth (Fig. 100). She is the second of four children; the others are normal. All lateral movements of the eyes were impossible; horizontal movements were unimpaired. There was a slight divergent strabismus with a myopia of 8 diopters in the diverging eye. Diplopia had never been present. Voluntary and involuntary movements of the facial muscles were impossible, with the exception of the ability to draw down the lower lip, which was done by both platysmal muscles; these functionated normally. The sternal portion of the left sternomastoid muscle was absent. The tongue was decidedly wrinkled and atrophic (Fig. 101), this and the paralysis of the lips being responsible for a slight dysarthria. The left arm was somewhat smaller than the right; the fingers were disproportionately small and one of them deformed (Fig. 102). The left breast and the underlying pectoralis major were absent (Fig. 103). The rest of the neurologic examination was practically negative. The patient stated that the maternal

grandfather and maternal uncle each had a small left arm, and that the latter was unable to use this arm for work. Practically all the members of the mother's family have syndactyly of the second and third toes.

Discussion.—Congenital defects of this kind are not only rare but also very interesting; they are as yet not very satisfactorily explained. Not all cases of congenital paralysis of the seventh nerve appear to be due to an absence of the motor

Fig. 100.—Case X (A270472). Congenital facial paralysis.

nuclei of these nerves. In some the nerve itself appears to be absent, while in others the possibility of a primary muscular defect must be admitted. In a number of cases associated deafness and a congenital atresia of the auditory canal is found. The diagnosis is usually easy, as the condition has been present since birth.

The features which characterize and distinguish the supranuclear or corticonuclear lesions of the facial nerve from the

infranuclear in many respects resemble the analogous paralyses seen elsewhere in the body; the former is essentially an involvement of the upper motor neurone, like a hemiplegia; the latter, a lesion of the lower motor neurone, as exemplified by neuritis or poliomyelitis. Extremely characteristic of a peripheral paralysis is the almost uniform involvement of all branches of the seventh nerve. Practically the only exceptions are found in partial

Fig. 101.—Case X (A270472). Dysplasia of the tongue associated with congenital facial paralysis.

lesions of the seventh nerve due to trauma about the face, and in hereditary facial paralysis, as exemplified in Case X. In the peripheral lesions of the seventh nerve alteration in the electric reactions also are obtained as a rule, particularly loss or diminution of response to faradic excitation and sluggish response to the galvanic current; these changes, however, do not develop until after the lapse of about fourteen days. The reflex activity is also absent or markedly impaired, seen, for example, in the

failure of the eyelid to close on irritation of the cornea. Occasionally fibrillary tremors are seen over the entire face and atrophy is easily discerned. In the greater number of cases, however, fibrillary tremors are absent and atrophy is not noticeable. In pontine lesions, including nuclear involvement of the seventh nerve, the clinical manifestation, par excellence, is a so-called hemiplegia alternans, in which the homolateral seventh and the heterolateral upper and lower extremities are paralyzed, a syndrome designated as the Millard-Gubler syndrome. The proximity of the sixth nerve usually leads to an associated ab-

Fig. 102.—Case X (A270472). Congenital malformation of the hands.

ducens paralysis on the same side. This type of paralysis is illustrated by Case VII.

Supranuclear lesions, on the other hand, usually show a marked difference in the degree of paralysis of the muscles of the forehead and those of the lower part of the face; the former, having supposedly a bilateral cortical representation, show little or no paralysis, while the latter, being innervated principally by cells of the opposite motor cortex, show a marked degree of motor impairment (Case VIII). Usually a hemiplegia also

affects the same side of the body. The electric reactions remain normal. Reflex action is preserved intact. Case IX illustrates another interesting feature, strikingly characteristic in pseudobulbar palsy, which is essentially a bilateral involvement of the upper motor neurones. While the patient cannot well perform voluntary movements, the movements associated with emotional expressions, such as laughing, crying, and so forth, are not only

Fig. 103.—Case X (A270472). Congenital absence of the left breast and the underlying pectoralis major.

present but also exaggerated. These impulses are supposed to arise in the paleo-encephalon, the developmentally older portion of the brain, namely, the basal nuclei, which after paralysis of the corticobulbar neurones assumes full and unchecked sway.

There are some other conditions in which the mobility of the facial muscles is impaired that are met with occasionally. The type of progressive muscular dystrophy (Landouzy-Dejerine) beginning in the muscles of the face and shoulder often

comes to a standstill for a number of years after involvement of the facial muscles before the progress of the disease is resumed in other muscles of the body. The onset of the disease, which is usually early in life, is very insidious, the progress is extremely slow, and in the main presents the characteristics of the other myopathies.

The Landouzy-Dejerine type of progressive muscular dystrophy is illustrated in Case XI.

Case XI (A247338).—Mr. E. H. M., aged thirty-seven, an auto salesman, came to the clinic complaining of difficulty in speech and swallowing. The family history revealed that the patient's father at the age of thirty-four had an illness with fatal termination, which in all respects resembled the patient's illness. His trouble began nine years before as a weakness in the lower lip. Within a few weeks he had some difficulty in closing the eyes and in speaking. The condition progressed slowly for about two years, when difficulty in rotating the left eye upward appeared. At this point his illness apparently came to a standstill until four months before examination. The patient had great difficulty in swallowing solids and choked easily; liquids troubled him less and every particle of solid food had to be washed down. He also had some difficulty in breathing, particularly on inspiration. He could not use his fingers readily, especially in cold weather, and was conscious of a slowly progressing, more or less general weakness.

Examination showed slight difficulty in rotating the left eye outward; when this was attempted objects at which he was looking became somewhat blurred. His face was mask-like. While he was able to wrinkle his brow fairly well, he could close his eyes only very slightly and movement of the lips was slight; he had much difficulty in drinking, as the liquid tended to wash between his lips and the glass. He was unable to whistle. Motor power of the jaw appeared to be normal. No movement of the soft palate could be noted on phonation. Laryngeal examination revealed a complete bilateral abductor paralysis; the tongue, although it could be moved somewhat, showed definite

diminution in strength and in amplitude. In speaking, the voice was somewhat husky and markedly nasal. Other findings were practically negative.

Discussion.—The appearance of facial paralysis, which progresses to a certain extent and then comes to a standstill for about five years, may give rise to some difficulty in the recognition of the underlying nature of the condition. The family history and the distribution of the paralysis, however, make the diagnosis relatively simple.

In myasthenia gravis the paralysis is usually most marked in the muscles about the face and jaw, but is by no means limited to these. Rapid fatigue, particularly of the extra-ocular muscles, the facial muscles, and the muscles of mastication, is a cardinal symptom, and a differentiation of this disease and other types of paralysis usually presents no great difficulty.

While scleroderma may localize largely in the face and lead to its immobilization, the attendant atrophy and distortion about the eyelids and lips prevent confusion with paralysis due to other causes.

PROGNOSIS

The course and the prognosis of the paralysis depend on an accurate determination of the underlying pathology. In the most common type of facial paralysis, that is, the so-called rheumatic type, improvement may begin within from one to three weeks; in the more severe forms restoration of function may begin in from three to four months or may not take place at all. Associated movements, due probably to misdirected regeneration of the nerve-fibers, have been discussed. Excessive lacrimation during the process of eating, which Oppenheim described in one of his cases, may perhaps also be attributed to this. At times a contraction appears in the muscles of the paralyzed side, which, at first glance, makes it appear as though it were the well side that had suffered paralysis. Movements on the originally paralyzed side, however, in spite of the contraction, are limited in amplitude and in power. Sometimes also only a portion of the nerve regenerates, for example, the fibers going to the eye, while those going to the other parts of the face

do not regenerate. Spasms may also appear which occasionally cause the patient more discomfort and embarrassment than the original paralysis.

Recurrences of facial paralysis are by no means uncommon. They often appear in patients having developmental defects, such as syndactyly, spina bifida occulta, hairy moles, etc., and for some unknown reason often localize in the opposite side of the face.

Not infrequently loss or diminution of sensibility, of hysteric origin, is present over the paralyzed side of the face; the failure of this to limit itself to the peculiar anatomic distribution of the fifth nerve gives it away. At times a weakness, functional in origin, of the same side of the body is seen.

The electric reactions are often an aid in determining the severity of paralysis. If after the lapse of from ten to fourteen days a response to the faradic current can be obtained and response to the galvanic closing and opening shocks is lightning-like, recovery usually takes place in from two to three weeks; if the faradic current produces contraction only by the employment of a very strong current or not at all, and the galvanic responses are swift, recovery may be expected in from one to two months; if no response is obtained on faradic stimulation, and response to the galvanic current is sluggish and creeping, recovery must not be expected within from one to six months, and may never occur.

TREATMENT

In the treatment of facial paralysis protection from exposure to cold is an important requisite. The local application of heat is often advantageous. Administration of salicylic acid preparations, such as aspirin, seems to be beneficial. Temporary splinting of the face by means of adhesive strips or fine threads anchored to the lower portion of the cheek and fastened in the hair has also been suggested as of value. Electrotherapy and gentle massage are often instituted with a certain amount of success. In case regeneration fails to take place or is not to be expected by reason of the underlying pathology, such as injury during parotid tumor operation, nerve anastomosis may be tried;

the spinal accessory or the hypoglossal nerve is the one usually selected. This often brings back symmetry to the face by means of the restoration of muscle tonus; occasionally a considerable degree of movement may be obtained by re-education, the patient having to learn to move the face by repeating in a mental way the old movements of the shoulder or the tongue, depending on the nerve selected for suture. Myoplastic operations, utilizing portions of the masseter or sternomastoid muscles, have been attempted with varying degrees of success. Occasionally, in case only one of the end branches of the facial nerve has been injured its fellow of the opposite side is cut for the cosmetic purpose of restoring symmetry.

THE CHEMICAL AND PHYSIOLOGIC NATURE OF THE ACTIVE CONSTITUENTS OF THE THYROID

E. C. KENDALL, PH. D.

DURING the past twenty-five years much research work concerning the thyroid has been carried out by surgeons, pathologists, and physiologists, and clinicians have collected a large amount of data, but in spite of all this work the quantitative results obtained have been meager. Advances in surgical treatment have met with opponents. Questions relating to hypertrophy and hyperplasia of the gland are subjects of heated debate between pathologists, and probably the greatest discord and variance of opinions of thyroid troubles is found among clinicians.

The several large clinics in this country that are treating thyroid disturbances have not been in accord with each other in regard to the relation between clinical symptoms and the histologic findings in the gland, nor have they agreed in regard to the best time and the desirability of surgical intervention. It is obvious that if all investigation were confined to surgical research, clinical examinations, and the microscope, ultimate conclusions with a quantitative value could not be secured. A barrier exists beyond which it is impossible to go without the aid of some other vehicle.

Problems in thyroid activity must be regarded as problems dealing with a physiologic process, and to interpret that process by its end-results may be misleading. The science which deals with the nature of matter and the amounts present is chemistry, and, since thyroid disturbances are merely alterations in the rate of a chemical process, it is only by chemistry that a clear understanding of the abnormalities can be explained, because it is only by a chemical analysis of the thyroid secretion that the

normal process can be established. Thyroid investigation was begun at this clinic in about 1906, and in 1908 Wilson and Plummer[13] established the fact that exophthalmic goiter is always accompanied with hyperplasia of the thyroid gland. This relationship is of great importance and marks a distinct advance in our knowledge of goiter, but, realizing that still more aid was required in this problem, a chemical investigation of the thyroid secretion was decided on; this study was begun by me in 1914.

Although extensive chemical investigation of the thyroid secretion had been carried out, no single crystalline substance possessing physiologic activity had up to this time been isolated from the gland. In 1895 Baumann established the important chemical fact that the normal thyroid contains iodin. He was able to concentrate the iodin compounds of the gland until a certain fraction contained about 9 per cent. of iodin. Beyond this partial purification he did not go. This fraction of the gland he named "iodothyrin." Other investigators immediately took up the problem, and at first iodothyrin was regarded as an active constituent of the thyroid. Later investigations have discredited this claim, however, and today iodothyrin is not regarded as even a concentrated form of thyroid gland. Desiccated thyroid has a certain definite and specific action on patients suffering from myxedema. Iodothyrin does not relieve the symptoms in the same way and to the same degree.

The proteins of the gland have been partially fractionated, and Oswald has separated a protein containing most of the iodin present in the gland, which he has named "thyreoglobulin." Thyreoglobulin possesses all the physiologic activity of desiccated thyroid, but it is not a single crystalline substance and its iodin content is not very much higher than that of desiccated thyroid. Although other investigators have partitioned the thyroid proteins into various fractions, these differ but little from iodothyrin, which is obtained by treating the proteins with acid, or from thyreoglobulin, which results from a separation of the proteins of the gland without any deep-seated destruction or alteration.

INVESTIGATION OF THE CHEMICAL CONSTITUENTS OF THE GLAND, WITH ISOLATION OF THE IODIN-CONTAINING COMPOUND IN PURE CRYSTALLINE FORM

Starting with fresh and desiccated thyroid the present investigation was at first concerned with the diffusibility of the iodin-containing compound. Iodin is not dialyzable from the thyroid proteins, and will withstand rather severe chemical treatment and still be undialyzable through a collodion sac in running water. In order to determine the stability of the iodin compound various hydrolytic processes were applied to the thyroid proteins. Among others the alcoholic alkaline hydrolysis used by Vaughan was tried, and with some slight modifications it was found to produce a deep-seated hydrolysis without breaking off iodin from its organic combination. Furthermore, the hydrolysis so alters the iodin-containing compounds that about 70 per cent. of the total iodin is dialyzable. Another change brought about by the hydrolysis is the solubility of the iodin compound in acid. About 50 per cent. of the total iodin contained in the hydrolyzed products is soluble in acids, and 50 per cent. is insoluble. The iodin in the acid-insoluble portion is, to a large extent, non-dialyzable. The presence of iodin in organic combination and in non-dialyzable form was encouraging evidence of the stability of the iodin compound and invited further investigation.

The physical and chemical properties of the acid-insoluble group of hydrolyzed constituents will be described somewhat in detail, since this will bring out the chemical problems involved and some of the difficulties encountered.

An alkaline solution of the acid-insoluble constituents is dark brown, almost black, with a green fluorescence, and shows a Tyndal phenomenon with a beam of light. The non-diffusibility, fluorescence, and Tyndal phenomenon show that the solution is one of colloidal nature. Among the acid-insoluble constituents are fatty acids, resulting from the original fat in the desiccated thyroid, and sulphur, which results from the decomposition of cystin. The solution has no characteristic odor other than a general fatty smell. The first step in the method

of separating the iodin compound is to dry the acid-insoluble constituents, mix with infusorial earth, and extract with petroleum ether to remove fatty acids and sulphur.

Later it was found that fresh thyroid glands could be substituted for desiccated thyroid as a source of material, and that hydrolysis in alcohol is not necessary. Hydrolysis of the proteins may be carried out by use of aqueous sodium hydroxid alone, and the length of the time can be reduced to twenty-four hours. A quantitative separation of all fats as sodium soaps may be affected, and a perfectly clear alkaline filtrate of the hydrolyzed thyroid proteins containing practically the entire iodin content of the gland is obtained. On acidification of this solution a fine flocculent precipitate separates. If this precipitate is filtered off and dried, it is found to contain approximately 0.1 per cent. of the total weight of the fresh glands used. It contains, on the average, 26 per cent. of the total iodin. The total iodin in the gland, therefore, is divided by aqueous alkaline hydrolysis into acid-soluble and acid-insoluble compounds. Approximately three-fourths of the total iodin-containing compounds are soluble in acid and only one-fourth insoluble. This proportion is remarkably constant during different periods of the year and in samples of thyroid from different species. The significance of the figure is not entirely clear, but in all probability it represents the equilibrium existing within the glands between the completed iodin compound which possesses physiologic activity and the materials which are used by the gland in the building up of the substance. Physiologically tested, the acid-soluble hydrolyzed constituents are inactive, and the small portion which is precipitated by acid possesses the entire physiologic activity of the gland.

The most striking property of the acid-insoluble group of hydrolyzed products is their acidic nature. They may be dissolved in alkali and reprecipitated by acid without appreciable loss of iodin.

Many attempts were made to separate the iodin compound by its solubility and precipitation properties with various reagents. No specific precipitant was found. No difference in

solubility was found which could be used to effect a separation. After many attempts to separate the iodin compound had failed, it became apparent that the compound was not present in free form, but was still firmly bound to some unknown substances. The iodin compound will be called thyroxin throughout this paper.

Without going into a detailed description of the separation of thyroxin the essential steps in the method consisted in the removal of impurities by the use of barium hydroxid and the insolubility of thyroxin in alcohol. Almost 200 mg. of the substance were isolated without difficulty and no trouble was anticipated in duplicating the results and separating any desired amount of thyroxin from the gland.

As the yield of thyroxin depends on the amount of desiccated thyroid which can be treated at any time, it was decided to enlarge our facilities for the hydrolysis of desiccated thyroid, which, up to this time, had been carried out in glass flasks. An 11-gallon galvanized iron tank was constructed to take care of 500 mg. of desiccated thyroid at one time. The acid-insoluble constituents were obtained as before, but no crystals of thyroxin were obtained.

After working for fourteen months in an endeavor to repeat the first isolation of the crystals, it was found that five conditions influence the isolation of thyroxin in pure crystallized form:

1. Effect of temperature on precipitation with an acid.
2. Effect of heating the alkaline hydrolysis solution in the presence of metal.
3. Effect of carbon dioxid.
4. Effect of temperature during treatment of a solution with carbon dioxid.
5. Effect of different samples of desiccated thyroid.

These five factors finally became apparent after a consideration of all the results obtained during the course of two years' investigation. It is remarkable that all these factors were unconsciously controlled during the first purification, especially as it took months to find out that many separate and distinct

influences were at work causing the destruction of the compound.

The investigation of the chemical constituents of the thyroid was begun by the writer in September, 1910. The use of barium salts to effect a separation was tried in November, 1914, and thyroxin was first isolated in December, 1914. Although more than 100 mg. were isolated at that time, it was not until February, 1916, that the effect of carbon dioxid was established and more of the substance was obtained. During the summer of 1916 several grams of thyroxin were separated, and in May, 1917, more than 7 gm. were available for its chemical identification. The empirical and structural formulas were determined during the summer of 1917. In December, 1917, Osterberg, working in this laboratory, succeeded in synthesizing a small amount of thyroxin. The synthesis was repeated and the structural formula confirmed in April, 1919. Up to the present time about 33 gm. of the compound have been separated from 6550 pounds of fresh thyroid material made up almost entirely of the thyroid of the hog.

After isolating about 7 gm. of thyroxin in the manner described, its empirical and structural formulas were determined, and the substance was shown to be 4, 5, 6 tri-hydro-4, 5, 6 tri-iodo, -2 oxy, -beta indolpropionic acid. Thyroxin exists in three forms: (1) the keto form with carbonyl group adjacent to the imino,

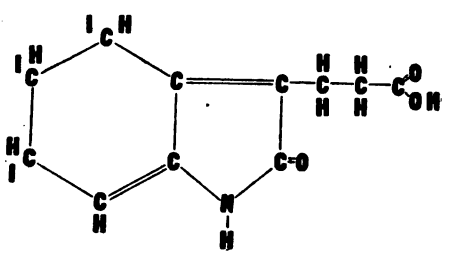


Fig. 104.

(2) a tautomeric enol form of this with an alpha hydroxy group and double-bonded nitrogen with no hydrogen attached to the imino,

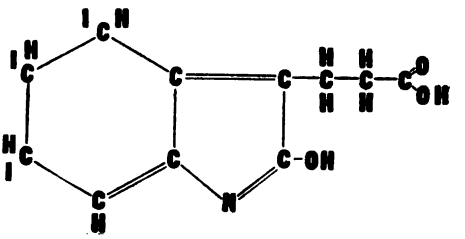


Fig. 105.

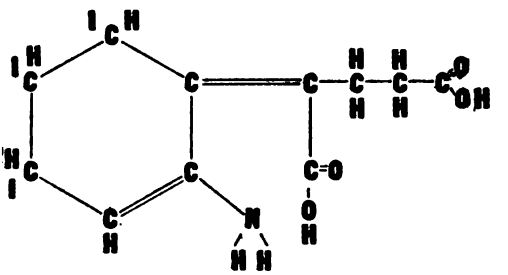


Fig. 106.

and (3) a form in which there is an open-ring structure, the elements of water entering between the imino and the carbonyl with the formation of an amino and a carboxyl group. A consideration of the isolation of thyroxin after its structural formula had been determined explains the chemical reactions involved in the purification and isolation of the substance.

Although it is not within the scope of this paper to consider at length the chemical formula and reactions of thyroxin, it is necessary to establish the chemical nature of the substance in order more fully to appreciate the physiologic activity of the substance when functioning in the animal organism. So long as thyroid disturbances were known only in clinical and surgical terms it was impossible to formulate and appreciate the chemical processes involved which brought about the clinical manifestations. Having isolated a single chemical substance in pure crystalline form the problem of thyroid investigation is tremendously simplified. The number of substances in the thyroid secretion which have physiologic activity has been a matter of some dispute. The relation of iodin to thyroid activity has

been a most debated subject. By the administration of thyroxin it has been possible to determine the exact physiologic activity of this substance and to determine whether or not any other substance is necessary in order to duplicate the physiologic activity of whole desiccated thyroid. It may be stated in brief that administration of thyroxin to a patient or experimental animal which is suffering from thyroid deficiency will relieve the symptoms to an extent, and in every detail in a manner similar to the administration of desiccated thyroid. It would appear, therefore, that there is no other substance present in the normal thyroid secretion which is essential for the physiologic activity of the gland.

In regard to the relation of iodin to thyroid activity it is evident that iodin is necessary for the physiologic activity of the normal gland. Thyroxin contains 65 per cent. of iodin and, as thyroxin is the active constituent of normal thyroid secretion, if any given gland contains no iodin the conclusion can be drawn that no thyroxin is present, and, therefore, the gland does not possess the physiologic activity of the normal thyroid secretion. It is necessary, however, to understand the chemical nature of thyroxin in order to appreciate what may occur in an abnormal thyroid secretion. The physiologic activity of thyroxin can be entirely destroyed merely by altering one atom of hydrogen within the molecule. If this is done the substance ceases to possess its usual physiologic activity. The iodin within the molecule is not affected by altering the atom of hydrogen. It is evident, therefore, that the activity of thyroxin is not due entirely to the presence of iodin within the molecule, and we are forced to conclude that the activity of the substance is in a large part, if not entirely, due to the unique configuration of the organic nucleus to which the iodin is attached. Altering the nucleus without affecting the iodin destroys its physiologic activity. The question still remains unanswered as to what would be the effect of substituting other elements for the iodin and leaving the organic nucleus intact. This question can only be approached through the field of organic chemistry, as it involves the synthesis of thyroxin and the building up in the laboratory

of the molecule piece by piece entirely independent of the animal organism and the thyroid gland, which is nature's way of manufacturing the material.

If the organic nucleus is the essential part of the thyroxin molecule, definite chemical reactions can and must be ascribed to thyroxin in order to explain what chemical processes are involved when thyroxin functions within the body. The possible chemical reactions in which thyroxin can be involved are centered around the amino group which is present within the molecule, and it seems highly probable that the function of thyroxin within the animal organism is to permit reactions involving acids and alkalis to take place at a much more rapid rate.

Without going into detail, thyroxin may be considered as a vehicle which is employed to transport a certain amount of material, for example, carbon dioxid, from one place to another.

The position occupied by thyroxin in the animal organism may be compared to the cylinder in a gasoline engine. The amount of energy produced at any time by the body is dependent on the capacity of the organism to produce energy, and Plummer has defined the function of the thyroid as the substance which determines the quantum of energy produced in the body. Considered in this way a quantitative relation can be established between the amount of thyroxin in the body and the amount of energy produced. If the size of the cylinder in a gasoline engine is increased or the length of the stroke increased the amount of energy produced bears a quantitative relation to the changes in the cylinder; in the same way the amount of thyroxin in the body determines how much energy the body is capable of producing.

In the absence of thyroxin other substances carry out this general process, so that the addition of thyroxin to the animal organism merely increases the rate of the chemical reaction. If thyroxin has entered into such a reaction it is regenerated at the end in its original form and is ready to react the second time. This cycle is kept up without interruption and the substance continues to function for a very long time, as much as three weeks after a single administration.

When for any reason a normal individual loses his thyroid secretion certain definite changes occur. Death is not produced by lack of a thyroid secretion, but the energy production of the individual drops to a level which is surprisingly consistent in all cases of high-grade myxedema. This level is 40 per cent. below normal, that is, the amount of energy which is produced in the body when at rest is 40 per cent. less than in a normal individual under the same condition. In order to explain this fact it is necessary to assume either that the rest of the cells within the body can produce sufficient thyroxin to maintain energy at the level of 40 per cent. below normal, or else that the cells in the body other than the thyroid do not produce an appreciable amount of thyroxin and life within the animal organism is maintained by substances other than thyroxin. Until the structural formula of thyroxin was known the first supposition would appear the more probable, but when the question is considered in the light of the known structural composition of thyroxin, the latter alternative is, in all probability, the correct one.

Thyroxin is an amino-acid. It is not like any other amino-acid; but still it may enter into reactions which are similar to those carried on by other amino-acids. In searching for the other compounds in the body which carry on reactions in a manner similar to thyroxin it is apparent that the most plausible substances are the compounds of similar chemical structure, that is to say, amino-acids and proteins, and to these may be added creatin and creatinin. No great significance can at this time be attached to the close resemblance in chemical structure, but as the chemical properties of thyroxin are more clearly understood it becomes more and more apparent that the physiologic activity of the substance is unique only in its ability to act as a catalyst.

There is no chemical reaction in which thyroxin enters that cannot be produced by other substances. The unique action of thyroxin lies in the fact that it can enter into a reaction and be regenerated at the end in its original form and in a manner which permits it to repeat the same reaction times without number.

The other substances of similar chemical structure are destroyed when they enter into reactions which are similar to the ones by which thyroxin produces energy.

Thus far only reactions concerned in the maintenance of the metabolic rate have been considered. It has been pointed out, however, by Guternatsch, Rogoff and Marine, Morse, Swingle, and others that desiccated thyroid and other iodin substances are capable of increasing the rate of the metamorphosis of the tadpole to the frog. This action has, furthermore, been shown to be due to the action of iodin. The metamorphosis of the tadpole, however, involves reactions which are undoubtedly different from the reactions involved in the maintenance of the normal metabolic rate.

The finding that iodin breaks off from thyroxin in the form of hypoiodous acids throws considerable light on this phenomenon. The action of the hypoiodous acid produced in the nascent state within the cells initiates a certain train of action which results in the differentiation of cells and metamorphosis of the larva form. This will not be considered in this paper except in so far as to point out that the effect of thyroxin on the metamorphosis of the tadpole and on the basal metabolic rate involves two separate and distinct chemical reactions.

Although the administration of thyroxin relieves the symptoms of hypothyroidism, in larger amounts it produces hyperthyroid symptoms and eventually death.

What chemical reactions are so stimulated by thyroxin that life is incompatible are still unknown; but it is obvious that death is not due, in a strict sense, to the presence of thyroxin itself, but is due to the secondary effects which thyroxin brings into play.

One of the most important findings in connection with the physiologic activity of thyroxin has been the establishing of the quantitative relation between thyroxin and the basal metabolic rate. Plummer has shown that 1 mg. of thyroxin in an adult weighing approximately 150 pounds increases the metabolic rate 2 per cent. The curve of this response has been shown to be approximately a straight line between metabolic rates 30

per cent. below normal to 15 to 20 per cent. above normal. This finding, coupled with the observation that all myxedematous patients tend to approach a uniform metabolic rate which is about 40 per cent. below normal, is extremely strong evidence in favor of the hypothesis that without the presence of thyroxin within the animal organism rapid and large fluctuations in energy output would be impossible. Clinically this is substantiated by the great difficulty the myxedematous patient manifests when endeavoring to walk upstairs or carry out any other muscular activity. The range of fluctuation of energy output is limited. The normal existence is at a rate in the neighborhood of 40 per cent. below normal. However, by the administration of thyroxin this basal metabolic rate can be raised to any desired figure, and it can be so maintained over periods of time measured in years. These facts suggest that in the normal animal organism thyroxin is not fundamentally essential to life. The fundamental chemical reactions occur and life is maintained in the complete absence of thyroxin, but in this condition the flexibility of energy output is limited to a narrow range. The addition of the thyroid apparatus to the animal organism establishes not only a higher plane of basal energy output, but it supplies the mechanism which permits the maximum range in flexibility of energy output.

The amount of thyroxin within the tissues is undoubtedly a physiologic constant, a figure as constant per weight of tissue as the normal number of red cells per cubic millimeter of blood, etc. What determines this normal content of thyroxin is unknown. What maintains the content of thyroxin within the tissues is obviously the blood-stream. Some work has already been completed in this laboratory which has the objective of determining the thyroxin content of the blood and tissues. This may be done by determining the maximum iodin content of the blood and tissues. Whether or not the total iodin in the blood and tissues is 100 per cent. in the form of thyroxin or 50 per cent. cannot be shown, but the total amount of thyroxin could not be more than the amount indicated by the total iodin present in the tissues. The method for the determination of

iodin which I published in 1914 has recently been further refined and perfected so that now 1 part of iodin in 10,000,000 to 20,000,000 can be determined with a high degree of accuracy. By the use of this method it has been shown that the iodin content of the blood of animals is approximately 1.5 to 2 parts per 10,000,000; that is, .015 to .020 of 1 mg. per 100 c.c. The iodin content of the tissues is slightly higher, averaging 2.5 to 3 parts per 10,000,000; and the content of the liver is still higher, from 3.5 to 4 parts per 10,000,000. These figures must be amplified and confirmed by more work, which is now being carried out, but they already indicate that there is an equilibrium existing between the amount of thyroxin in the blood, in the tissues, and in the liver.

If the presence of thyroxin within the tissues determines the metabolic activity of the tissues, it is obvious that if there were no mechanism for varying the amount of thyroxin and if the tissues always contained enough thyroxin to permit of their maximum output of energy, the control of the energy output during periods of rest would be, to say the least, difficult. Whether or not the thyroxin content of the tissues diminishes after a period of great exertion, the thyroxin being carried back to the thyroid gland by means of the blood-stream and there held as a reservoir until further demanded, is still unknown.

This mechanism is at least indicated and is in part substantiated by the findings of the seasonal variation of the iodin in the thyroid gland. Seidell and Fenger have shown that during the winter months the thyroid glands of beef, sheep, and hogs all contain much less iodin than during the summer months. It is apparent that during the winter months more energy is required to maintain body temperature, and the low iodin content of the gland could be explained either by the fact that the thyroid gland has given up its supply of thyroxin to the tissues or by an actual wearing out of thyroxin due to the prolonged functioning of the substances in the tissues, so that during January, February, and March the amount left in the gland would be at a minimum. During the summer months, with less energy production in the animal, the amount of thyroxin demanded in

the tissues is less. It reappears in the gland, either because its rate of production is greater than its rate of destruction, or because the amount in the tissues is returned to the gland and held there for use at some future time. The seasonal fluctuation of thyroxin in the gland is more satisfactorily explained on this basis than on the basis of varying iodin content of the food,

Fig. 107.—Case 118156. At time thyroxin treatment was begun and six months later. Increase in height 4 inches.

and as it holds for beef, sheep, and hogs, it is suggestive that the mechanism of the variation is essentially due to the varied energy output of the animals during the cold and the hot months of the year.

The physiologic activity of thyroxin and its effect on the animal organism have been established by studying the reactions

in normal dogs and in patients suffering from myxedema. No detailed account of these experiments will be given here, but it may be of interest to record two typical cases, one of a cretin, the other of a patient suffering from myxedema.

Fig. 108.—Case 118156. At time thyroxin treatment was begun and one year later. Increase in height 6 inches.

CASE I (118156).—L. M., a girl aged ten, came to the clinic suffering from thyroid deficiency. The child had not received desiccated thyroid at any time up to the age of ten. She was brought for examination because of her stunted growth; she was 37 inches high and weighed 37 pounds (Figs. 107, 108).

During three months she was given all the constituents of

the thyroid other than thyroxin. This produced no visible effect. She did not grow any taller and there was but slight change in her skin and general appearance. She was then given 0.4 mg. of thyroxin every day for six months, during which time she grew 4 inches. She has continued to take thyroxin in doses varying from 0.4 to 0.8 mg. up to the present time. A table of her heights and weights is as follows:

Date.	Weight, pounds.	Height, inches.
January 4, 1915	37	37
January 27, 1915	35⅛	38
February 27, 1915	36¾	38
April 2, 1915	38	39
May 5, 1915	37	39
June 4, 1915	37½	39¾
July 8, 1915	39	41
August 5, 1915	41½	41½
September 4, 1915	41½	41¾
October 16, 1915	42¾	41¾
November 13, 1915	45	42
December 14, 1915	44¾	42¼
January 16, 1916	45½	43
February 15, 1916	44	43¼
March 17, 1916	45½	43¾
April ?, 1916	43	43¾
May ?, 1916	46	44
June 18,.1916	47	44⅛
July 14, 1916	46½	44½
August 16, 1916	47½	45¼
September 17, 1916	48½	45½
October 22, 1916	50	45½
November 17, 1916	50½	45¾
December 6, 1916	50½	45⅝
January 16, 1917	52	46
March 13, 1917	52	46½
April 19, 1917	53	46¾
May 25, 1917	54	46¾
June 19, 1917	53	47
July 23, 1917	53	47
August 22, 1917	53	47¼
September 25, 1917	54	47¾
October 29, 1917	56	47¾
November 27, 1917	57	48
December 20, 1917	56	48⅛
January 16, 1918	57	48⅛
February ?, 1918	58	48⅛

Date.	Weight, pounds.	Height, inches.
March 30, 1918	58½	48⅓
April 20, 1918	59	48⅓
May 30, 1918	58½	48½
June 26, 1918	58	48½
July 21, 1918	57½	48½
August 30, 1918	58	48½
September 24, 1918	57	48¾
October 28, 1918	58	49
November 30, 1918	58½	49½
December 31, 1918	58	49¾
January 31, 1919	59½	50¼
February 27, 1919	60	50¼
March 23, 1919	62	50¼
April 27, 1919	60	50½
June 22, 1919	59½	50½
August 29, 1919	65	52½

Today this child is bright and active; she attends school and is restored as nearly to normal as is possible, considering the late time in her life when thyroid medication was started. She has received nothing but thyroxin, and all the improvement is due to this single substance. The patient not only grew taller, but also her skin became soft and moist; her hair, which was coarse and thin, became thicker, softer, and much longer; her mentality is wonderfully improved.

This patient is a typical example of the way in which thyroxin affects the animal organism. No cell in the entire body remained unchanged. Every cell was stimulated to greater activity. In this connection it is also to be noted that the patient was not given excessive amounts of thyroxin. An overdosage of the substance produces effects that are almost as deleterious as an absence of thyroxin.

The amount of thyroxin given an individual depends on the rate at which that individual destroys thyroxin, and only enough should be given to maintain a normal balance, that is, the patient's production of energy should be regulated so that it is neither above nor below the amount which is normal for the weight and height.

CASE II (146434).—Mrs. S., aged forty-seven, came to the clinic chiefly because of her mental symptoms. This patient, a

woman of high social position, well educated, and financially independent, had become slowly incapacitated during the past ten years, and at the time of examination had ceased practically all activities. She required a trained nurse, at times was irrational, and had spent about six months in a sanitarium, with a diagnosis of dementia præcox, and a hopeless prognosis (Figs. 109, 110).

We administered large amounts of thyroxin for three weeks, and the patient was entirely relieved; the edema and subjective symptoms had disappeared, and she was bright and alert. She

Fig. 109.—Case 146434. Patient at the time thyroxin treatment was begun and one month later.

returned home to take up her household management, and since that time has been practically normal.

Although the mental condition of this patient was her reason for coming to this clinic and was perhaps her most striking abnormality, still, the administration of thyroxin produced a change throughout her entire body. She is now taking approximately 8 mg. of thyroxin each week. More or less than this amount produces subjective symptoms.

A correct diagnosis had not been made elsewhere because desiccated thyroid had been given and produced no improve-

ment in the symptoms. This may be explained by the fact that a large amount was necessary in order to initiate the improvement. Very large doses of thyroxin were required during the first few days, but after the first response the patient became as sensitive to thyroid medication as the normal person. This probably is due to the patient's non-absorption of the material

Fig. 110.—Case 146434. Same as Fig. 109, side view.

from the alimentary tract. After the improvement had been brought about this absorption improved, and the patient reacted in a normal manner.

BIBLIOGRAPHY

1. Baumann, E.: Uber das normale Vorkommen von Jod in Thierkörper, Ztschr. f. physiol. Chem., xxi, 319–330, 1895, 1896.
2. Gudernatsch, J. F.: Studies on Internal Secretion. IV Treatment of Tadpoles with Thyroid and Thymus Extracts, Anat. Rec., xi, 357–359, 1916, 1917. Feeding Experiments with Tadpoles, II. A Further Contribution to the Knowledge of Organs with Internal Secretion, Amer. Jour. Anat., xv, 431–482, 1913, 1914.
3. Kendall, E. C.: The Physiologic Action of Thyroxin, Endocrinology, iii, 156–163, April–June, 1919.
4. Kendall, E. C.: Isolation of the Iodin Compound which Occurs in the Thyroid, Jour. Biol. Chem., xxxix, 125–147, August, 1919.

5. Morse, M.: The Effective Principle in Thyroid Accelerating Involution in Frog Larvæ, Jour. Biol. Chem., xix, 421–429, 1914.
6. Osterberg: Personal communication.
7. Oswald, A.: Zur Kenntnis des Thyreoglobulins, Ztschr. f. physiol. Chem., xxxii, 121–141, 1901.
8. Plummer, H. S.: The Thyroid Hormone and its Relation to Metabolism. Presented before the Association of American Physi ians, Atlantic City, May 6, 1918.
9. Rogoff, J. M., and Marine, D.: Effect on Tadpoles of Feeding Thyroid Products Obtained by Alkaline Hydrolysis, Jour. Pharmacol. and Exper. Therap., ix, 57–73, October, 1916.
10. Seidell, A., and Fenger, F.: Seasonal Variation in the Iodin Contents of the Thyroid Gland, Jour. Biol. Chem., xiii, 517–526, 1912, 1913
11. Swingle, W. W.: Iodin and the Thyroid. III. The Specific Action of Iodin in Accelerating Amphibian Metamorphosis, Jour. Gen. Physiol., i, 593–606, July 20, 1919.
12. Vaughan, V. C., Vaughan, V. C., Jr., and Vaughan, J. W.: Protein Split Products in Relation to Immunity and Disease, Philadelphia, Lea and Febiger, 474 pp., 1913.
13. Wilson, L. B.: The Pathologic Changes in the Thyroid Gland as Related to the Varying Symptoms in Graves' Disease: Based on the Pathologic Findings in 294 cases, Amer. Jour. Med. Sci., cxxxvi, N. S., 851–861, December, 1908.

THE VALUE OF THE BASAL METABOLIC RATE IN THE TREATMENT OF DISEASES OF THE THYROID

W. M. Boothby, M. D.

The object of the demonstration this afternoon is, first, to explain briefly what is meant by the term "basal metabolic rate," second, to describe the method of its determination, and third, to illustrate the clinical value of the basal metabolic rate in the treatment of thyroid disorders.

EXPLANATION OF THE TERM "BASAL METABOLIC RATE"

"In each mammal there is a basal metabolism." By the term "basal metabolism" of an organism is meant the minimal heat production of that organism, measured from twelve to eighteen hours after the ingestion of food and with the organism at complete muscular rest. This minimal heat production may be determined directly by actual measurement by means of a calorimeter, or indirectly, by calculating the heat production from an analysis of the end-products which result from oxidation within the organism or specifically, the amount of oxygen used and the corresponding amount of carbon dioxid produced, together with the total nitrogen eliminated in the urine.

The determination of a patient's basal metabolic rate is, therefore, like the taking of his temperature, the measurement of certain heat phenomena inherent in the living organism. The basal metabolic rate, as I have said, is the amount of heat produced by a person under certain standard conditions; while the temperature is the measurement of the heat level, or the balancing point between heat production and heat elimination, and is expressed in standard units, as degrees Centigrade or Fahrenheit. Let me illustrate my meaning by some physical experiments. Here is a beaker of distilled water heated by one Bunsen burner; the water is boiling moderately, and the thermometer therein registers 100° C. The second beaker of water is heated

by two Bunsen burners, the water is boiling more violently than in the first beaker, but the thermometer therein registers the same temperature, 100° C. And, finally, under this third beaker we have one Bunsen burner turned very low and the flame appears about one-half the size of that under the first beaker. The water is just boiling, or "simmering," and again the thermometer registers 100° C. Obviously, there is a great difference in heat production in the three experiments, but the thermometer gives us no clue to these differences because the regulatory mechanism of the boiling maintains the heat level at the same constant point. However, by adding salts to the water or varying the atmospheric pressure on the surface of the water, changes can be made in the boiling-point.

Under normal conditions the heat regulatory mechanism of all warm-blooded animals is so exquisitively sensitive and accurate that it maintains the body at a constant normal temperature. There are many diseases, mostly of bacterial character, that upset this regulatory mechanism, and increase the temperature of the body, just as the addition of salts raises the boiling-point of water. The diagnosis, treatment, and prognosis of febrile disorders have been rendered far more exact by the use of the thermometer; no one will for an instant question its value. But, on the other hand, the thermometer gives us no information as to the diagnosis, treatment, or prognosis (except for intercurrent infections) of a very much larger group of diseases. However, in this group there are certain diseases which show marked variations in the amount of heat produced. The most striking variations are found in disorders of the thyroid gland. In patients suffering from hyperthyroidism the basal metabolic rate, or heat production, may be more than twice that of the normal person, representing the physical example of two Bunsen burners, while in hypothyroidism or myxedema the rate may be one-half normal, corresponding to the Bunsen burner turned low.

As a general rule in febrile disorders the higher the temperature, the more intense the infection, so in hyperthyroidism the higher the basal metabolic rate, the more severe the dis-

ease. But, as we all know, the patient who has a temperature of 104° F. will not necessarily die; nor, on the other hand, will the patient with a temperature of 102° F. necessarily live, for other factors play their part. And so in evaluating the basal metabolic rate we must take into consideration other factors, such as the condition of the heart, loss or maintenance of weight, and ability to take nourishment. Still the chief proposition remains, that the higher the rate in hyperthyroidism, the more severe is the disease, and, conversely, the lower the rate in hypothyroidism, the more complete is the decrease in function of the thyroid gland.

DETERMINATION OF THE BASAL METABOLIC RATE

Time prevents me from entering into a discussion of the fundamental principles of indirect calorimetry and their development; it will suffice to state that the heat produced by the combustion of any substance, whether or not in a living body, can be determined from a knowledge of the quantity of oxygen consumed together with the end-products of that oxidation. The routine method of determining the basal metabolic rate as used in our laboratory is as follows:

To eliminate the influence of food the patient comes to the laboratory in the morning without breakfast, in the so-called postabsorptive state. He is put to bed and comfortably arranged; he lies quiet for twenty minutes so that the influence of muscular exertion will cease. During this preliminary period the pulse, respiration rate, and blood-pressures are taken.

The test proper is begun after this twenty minutes' rest, when a mask is tied on the patient's face. The total expired air is collected by means of inspiratory and expiratory valves, over an accurately timed period, approximately ten minutes. The volume of the expired air is carefully measured and the temperature and barometric pressure recorded. Samples of the expired air are analyzed in duplicate to determine the percentage of oxygen and carbon dioxid. We now have sufficient data to calculate the total hourly heat production with an error of less than 1 per cent. Du Bois has shown that the heat produc-

tion of a person is proportional to his surface area, a factor dependent on his height and weight. The calories for each square meter of body surface for one hour thus found are compared with Du Bois' normal standards of comparison which are dependent on the age and sex of a patient. The results are reported to the clinician in terms of percentages above and below normal. We do not consider variations in the basal metabolic rate of $\pm$ 10 per cent. of clinical significance.

The case histories which I shall present illustrate the clinical use of the basal metabolic rate for diagnosis, prognosis, and treatment in thyroid disorders. The first case is one of mild hyperthyroidism in an otherwise neurotic patient, and illustrates the value of the basal metabolic rate at two periods in the course of the disease in determining the presence or absence of hyperthyroidism.

CASE I (A230712).—Mrs. C. W. O., aged forty-two, came to the clinic May 5, 1918, complaining of itching of the skin, weakness, and heart trouble. She was first assigned to the Dermatologic Section, and the positive findings were as follows:

A well-built, somewhat undernourished woman who has lost 10 pounds in the past month in spite of a good appetite. There is marked dermagraphia; the face has a cyanotic appearance; chest and back show a few papules and pustules; the thyroid is large and hard; there is a fine fibrillary tremor of the tongue and a coarse tremor of the extended hand; palpitation of the heart; no murmurs; pulse 108; Wassermann reaction negative; skin sensitization tests negative. The dermatologic diagnosis of chronic urticaria was made and the patient referred to a section of general medicine for further study.

The Medical Section elicited the following additional positive data: About nine months ago, after a hard day's work in the heat, the patient became very nervous and generally upset, with severe pain on the left side of the head for three or four days, together with palpitation of the heart. Since then her heart has been very irregular, with attacks of palpitation of short duration, occasionally accompanied by shortness of breath

and faintness. The general physical examination was negative. The urine showed a trace of albumin.

The patient was then seen in consultation and transferred to Dr. H. S. Plummer's section, where, in addition to the above, it was found that since the onset of the present illness nine months before loss of weight and strength had been progressive in spite of a good appetite. Recently the patient had been getting out of breath very easily on exertion. It was especially difficult for her to go up and down stairs, indicating loss of strength in the quadriceps muscle. It was also learned that the patient had had a goiter at the time of puberty which disappeared under treatment. The symptoms were tabulated as follows:

Nervousness began nine months before, maximum severity now 2
Tremor began two months before, maximum severity now... 3
Dyspnea began nine months before, maximum severity now 1
Palpitation began nine months before, maximum severity now 2
Tachycardia began nine months before, maximum severity now..... 2
General loss of strength began two months before, maximum severity now..... 2
Quadriceps loss at present distinct..... 2
No vomiting.
No diarrhea.
Insomnia began nine months before, maximum severity now 2
Increased sweating began five weeks before, maximum severity now..... 1
No edema.
No headache.
Skin diffusely pigmented and hyperemic.
Normal weight 135 pounds, present weight 118 pounds (with clothes).
No exophthalmos. Stellwag, 0; Möbius, 0; von Graefe, 0.
Patient had not noted goiter or enlargement of neck except at the time of puberty.
No evidence of local pressure on the neck.
Right lobe thyroid 1 by 3½ cm.; left lobe 1 by 3½ cm.; a small adenoma in the median lobe.
No thrills or bruits.
Heart: Right border 3½ cm. from midsternal line; left border, 16 cm.; apex, 9 cm.
Pulse-rate 124, systolic blood-pressure 140 mm., diastolic 86 mm. in examining room.
Basal metabolic rate +29 per cent. with pulse-rate of 98, systolic 122 mm., diastolic 74 mm., in bed. Weight, 114½ pounds.

The onset of hyperthyrodism had occurred nine months before examination, with a gradual development to the present severity. A diagnosis was made by Dr. H. S. Plummer of exophthalmic goiter due to hyperplasia of the thyroid gland.

The patient was sent to the Colonial Hospital, and after six days' preliminary rest in bed a thyroidectomy was performed (June 3, 1918). The right lobe and isthmus and about one-half of the left lobe were resected, leaving a piece on the left side equal to about three-fourths of a normal lobe. The enlargement of the right lobe was about twice the normal size and on the left one and one-half times normal. One tube drain was inserted in the wound.

The pathologic diagnosis was hypertrophic parenchymatous thyroid, exophthalmic goiter. The pathologic specimen measured 6 by 4 by 3 cm. and weighed 40 gm.

There was a moderate postoperative reaction in pulse and slight febrile reaction, with rapid return to normal. The patient left the hospital six days after operation, and was discharged from the clinic June 15, 1918.

November 23, 1918, the patient reported by letter that for three months after the thyroidectomy she was much better, but that recently her heart had begun beating hard and "feels as though the bottom had dropped out," together with a "choking sensation as though something were tied around the throat."

January 9, 1919, the patient returned to the clinic for examination. She complained of an almost constant choking sensation, most noticeable if she was upset. She was annoyed by the pounding of her heart, and she still had some dyspnea on exertion. She had steadily gained in weight (18 pounds), her appetite was good, and she slept well. The urticaria had been better for several months following the operation, although it was now troubling her again.

On examination the pulse was found to be 88, the systolic blood-pressure 138 mm., and diastolic 88 mm. The general physical examination was negative; the weight 128½ pounds. The basal metabolic rate was −3 per cent., the pulse 73, systolic

120 mm., and diastolic 80 mm., in bed. A diagnosis of neurosis with globus hystericus was made.

This patient illustrates:

1. A case of mild exophthalmic goiter superimposed on a neurosis. The otherwise questionable existence of hyperthyroidism was rendered certain by the increased metabolic rate of +29 per cent. and was confirmed by the pathologic examination of the excised gland.

2. A postoperative condition of neurosis with globus hystericus in many ways simulating hyperthyrodism, but with the latter condition absolutely ruled out by the normal metabolic rate.

3. The relief by operation of the symptoms caused by hyperthyroidism, while the symptoms due to the neurotic condition remained unimproved. The patient had gained in weight, the heart rate and the blood-pressure had decreased, and the basal metabolic rate had returned to normal, although there was no improvement in the neurotic symptoms, such as choking and distress about the heart.

Case 230712, Mrs. C. W. O., aged forty-three.

Clinical diagnosis: Exophthalmic goiter, chronic urticaria.

Pathologic diagnosis: Hypertrophic parenchymatous thyroid (exophthalmic goiter).

	Basal metabolic rate, per cent.	Respiratory quotient.	Systolic, mm.	Diastolic, mm.	Pulse pressure.	Pulse.	Temperature.	Weight, kg.
5/17/18.....	+29	0.73	122	74	48	98	98.6° F.	51.9
6/3/18..Thyroidectomy								
1/10/19.....	−3	0.81	120	80	40	73	98.6° F.	58.3

At one stage in this case the presence of hyperthyroidism was rendered definite by the increased basal metabolic rate; at another stage the existence of hyperthyrodism was ruled out by the metabolic determination which was within normal limits. We

consider that the basal metabolic rate differentiates thyroid intoxication from neurosis simulating hyperthyroidism just as definitely as does the thermometer determine the presence or absence of a febrile condition.

The second case I shall present is a typical case of severe exophthalmic goiter with a high basal metabolic rate which showed the characteristic decrease following two ligations and thyroidectomy.

CASE II (A239096).—Mrs. G. B., aged fifty-one, came to the clinic July 23, 1918, on account of enlargement of the neck, which was first noticed seven months before at the time of menopause, since when the size of the neck had increased gradually and the patient had had moderate difficulty in swallowing. Three months previous to examination the patient had noticed that she was becoming more nervous, and that her body was warmer, with an increased amount of perspiration. Loss of strength had been marked, dyspnea on exertion had increased during the last three months, and she had lost about 30 pounds in weight, although her appetite had been good. Six weeks before she had had an attack of diarrhea for one week and again during the past week.

On examination the pulse-rate was found to be 122 and regular; the systolic blood-pressure was 132 mm., the diastolic was 63 mm.; the heart was slightly enlarged, the hemoglobin was 61 per cent., the urine contained a trace of albumin, with a few pus-cells; there was slight edema of the legs, the skin was moist, the teeth were bad, and the tonsils contained pus. The following tabulated information with regard to the symptoms of goiter was made:

Nervousness began four months before, maximum severity now	2
Tremor began two months before, maximum severity now	2
Dyspnea began three months before, maximum severity now	1+
Palpitation began three months before, maximum severity now	1+
Tachycardia began ? , maximum severity now	2

Loss of strength began four months before, maximum severity now..... 2
Quadriceps loss began three months before, maximum severity now..... 3
No vomiting.
Diarrhea, attack of one week's duration six weeks before, and again now.
Insomnia began one week before, with maximum severity now..... 1
Sweating began one and a half months before, with maximum severity now..... 2
Edema began three months before, with maximum severity three months before, 4; present severity..... 1+
Loss of weight 18 pounds, weight now 138 pounds (with clothes).
Exophthalmos now, right 1, left 1. Möbius' sign +.
Goiter first noticed seven months before, with gradual development.
Thyroid, right 6 cm. by 4 cm.; left 2¼ cm. by 1¾ cm.
Thrill, right superior 2, left superior 1, right inferior 0, left inferior 0.
Bruit, right superior 2, left superior 1, right inferior 2, left inferior 1.
Heart, right, dull, 1 cm.; left 10 cm., no murmurs, regular 122, systolic 132 mm., diastolic 63 mm. in examining room.
Hyperthyroidism, definite onset two months before, probable onset four months before, possible onset seven months before, maximum severity now..... 2+
Basal metabolic rate +80 per cent., pulse-rate 111, systolic 118 mm., diastolic 48 mm., in bed. Weight 130¾ pounds.
Diagnosis: Exophthalmic goiter, hyperplasia of the thyroid with marked intoxication.

July 29, 1918, the patient was admitted to the hospital for rest and observation. After eight days' rest in bed the basal metabolic rate fell from +80 to +71 per cent., and after four more days in bed the rate fell to +63 per cent. This drop in the basal metabolic rate corresponded with the improvement in the general clinical symptoms. The charted pulse-rate the first week averaged about 90 and at the end of the second week about 85. The temperature curve ran slightly below normal, about 98° F.

August 12, 1918, division with ligation of the left superior thyroid vessels with catgut was performed. For three days there

was slight reaction in temperature to 100° F., and in pulse to 100, then a gradual fall to the former level. On the eighth day after ligation the basal metabolic rate was +64 per cent., showing no further immediate improvement. August 21st division with ligation of the right superior thyroid vessels was done with catgut. For three days there was a slight increase in temperature and pulse. The patient was allowed to leave the hospital on the sixth day after the second ligation; her temperature was normal and pulse-rate 82; she was allowed to go home on the twenty-ninth day, to return in three months for thyroidectomy. No metabolic rates were determined before the patient's discharge after the second ligation, as her general condition was showing improvement.

November 8th the patient reported by letter, "I feel fine now, only a little nervous and have gained 14 pounds in weight." December 12th she returned for thyroidectomy. She had gained a great deal in strength; the quadriceps loss was 1+ instead of 3. She was sleeping well, her appetite was good, and she had had no nausea, vomiting, or diarrhea. Her ankles were still slightly edematous. The left border of the heart had decreased to 8 cm. The pulse-rate was 102, in the examining room, and the systolic blood-pressure 150 mm., diastolic 70 mm., the weight 145 pounds, with clothes. The basal metabolic rate was +47 per cent., a very decided improvement, the pulse-rate in bed 96, the systolic blood-pressure 128 mm., the diastolic 60 mm., and weight 134¼ pounds.

The patient was sent to the hospital, and after a week's rest the pulse-rate fell to 90. Thyroidectomy was performed December 18th, with removal of practically all the right lobe and isthmus, and resection of the left lobe. A piece of gland tissue was left equivalent to practically three-fourths of a normal sized lobe on the left, the muscles were cut on the right, and one tube drain inserted.

The pathologic diagnosis was hypertrophic parenchymatous thyroid, exophthalmic goiter. The pathologic specimen measured 13 by 6 by 3 cm., and weighed 100 gm.

Following the operation the temperature rose to 102° F.,

the pulse to 130; by the seventh day they had gradually fallen to 98° F. and 84 respectively, at which time the patient was allowed to leave the hospital. January 4, 1919, the basal metabolic rate was determined and found to be +12 per cent.; the pulse-rate, with the patient in bed, was 83, the systolic blood-pressure 120 mm., the diastolic 60 mm. She was discharged from the clinic January 6, 1919.

This patient illustrates a severe case of exophthalmic goiter with an original basal metabolic rate of +80 per cent., followed by definite improvement at each stage of the treatment. The indications of improvement gained from clinical observation parallel the gradual and progressive decrease in the basal metabolic rate to a practically normal reading.

Case 239096, Mrs. G. B., aged fifty-one.

Clinical diagnosis: Exophthalmic goiter.

Pathologic diagnosis: Hypertrophic parenchymatous thyroid (exophthalmic goiter).

	Basal metabolic rate.	Respiratory quotient.	Systolic, mm.	Diastolic, mm.	Pulse pressure, mm.	Pulse.	Temperature.	Weight, kg.
7/25/18.....	+80	0.71	118	48	70	111	99.3° F.	59.4
7/29/18 Admitted to hospital								
8/6/18.....	+71	0.78	130	60	70	104	98.4° F.	53.5
8/10/18.....	+63	0.74	130	46	84	102	98.7° F.	53.3
8/12/18 Ligation								
8/20/18.....	+64	0.77	132	65	67	113	97.9° F.	53.2
8/21/18 Second ligation								
12/6/18.....	+47	0.75	128	60	68	96	97.8° F.	61.0
12/18/18 Thyroidectomy								
1/4/19.....	+12	0.80	120	60	60	83	97.6° F.	58.1

The amassing of large numbers of similar cases in which the clinical improvement at each stage is outstanding and beyond question accompanied by a marked lowering in the basal metabolic rate, has given us confidence in accepting all decreases in

the basal metabolic rate as indicative of a corresponding improvement in the patient's general condition, although occasionally there may be no other positive evidence of such improvement. We have come to this interpretation in the same way that in years past the clinician learned to realize that a decrease in temperature during a febrile disease indicated, except just before death, an improvement in the patient's condition, the degree of improvement corresponding to the degree of the decrease in temperature.

In contrast to the condition of hyperthyroidism, illustrated by the preceding cases, is the syndrome of hypothyroidism due to partial or complete inactivity of the thyroid gland. Extremely important work has been done in the last two years by Dr. H. S. Plummer in the use of the basal metabolic rate in the diagnosis and treatment of myxedema. He has found that in the most advanced cases of myxedema in which, as nearly as can be judged, the thyroid is inactive, the basal metabolic rate is between −35 and −40 per cent., and that gradations of the thyroid insufficiency up to normality can be identified with the aid of the basal metabolic rate. In cases in which a mild myxedematous condition is suspected the clinical diagnosis is confirmed by a basal metabolic rate below −15 per cent. Such cases can now be diagnosed at a very early stage and, therefore, treatment may be started long before it would otherwise be possible. Plummer has also been able to simplify and render definite and exact the treatment of myxedema by the use of Kendall's thyroxin, the active principle of the thyroid gland, which admits of very accurate dosage. The thyroxin can be administered either by mouth or intravenously; the latter method is preferable while the patient is at the clinic, while the dosage is being accurately gaged, and to obtain results as rapidly as possible. Oral administration is suitable for the continued and, usually, lifelong use. As Plummer has shown in many cases, 1 mg. of thyroxin will increase, on the average, the basal metabolic rate in cases of complete myxedema by 2 per cent.; that is, the intravenous administration of 15 mg. thyroxin will, as a rule, increase the basal metabolic rate from −40 to −10 per cent., thus by one dose bringing

the patient to within the limits of normal metabolic variations. The effect of the thyroxin is usually first detectable from eight to ten hours after administration; the maximum effect is reached in the second week after injection and several weeks elapse before the full effect of the thyroxin has worn off and the basal metabolic rate returned to the original low reading. The demonstration of this delayed and long-continued action of thyroxin explains many of the difficulties encountered in obtaining the correct thyroid dosage. In fact, we consider that it is impossible properly to treat such cases without regulating the dosage by frequent basal metabolic rate determinations, by means of which the administration of thyroxin can be so regulated as to keep the basal metabolic rate within the limits of normal variation. Some of the points just mentioned are illustrated by the following case:

CASE III (A285377).—L. A. S., a physician, aged fifty-three, came to the clinic August 20, 1919, complaining of anemia. Four years before the patient began to lose his 'pep"; there was loss of strength, especially marked in the right leg, and gradually becoming more general, although the patient said that he was still able to mow the lawn. Simultaneous with the loss of strength, his hands, the palms of which were at first noticeably moist, became very cold, and for the past three years the skin has been dry and scaly. He complained of cold feet and numbness of the extremities. He first noticed the puffiness of his face two years before. Within the last year he had become quite deaf, and his acuity of vision had diminished. For the past six months he had been very sleepy during the day. He said he did not sleep well and complained of strangling sensations when he did sleep, apparently due to relaxation of the palate. He had considerable aching in his joints, knees, ankles, and feet, first noticed a year and a half ago and now quite severe. The patient stated that he had sung a low bass, but gradually had lost his voice, and it had become coarse and weak.

On physical examination the edema or puffiness, so characteristic of a myxedematous condition, was evident and there

was free fluid in the abdominal cavity. The patient had an extremely pasty yellow skin, dry and scaly, especially on the back of his hands. Muscular weakness was apparent and his gait could best be described as a "duck-like waddle." His tongue was thick, causing indistinctness in articulation, and his speech slow.

In the examining room the systolic blood-pressure was 98 mm., the diastolic 72 mm., the pulse-rate 84. The urine was negative. The hemoglobin was 69 per cent.; erythrocytes 4,150,000, and leukocytes 10,200. The Wassermann reaction was negative. The examination of the central nervous system was negative. Examination of the teeth showed general oral sepsis. The vision of the right eye was 60/30, and of the left, 6/10; the fields were normal and the fundi negative, but there was chronic conjunctivitis. The tonsils were slightly enlarged, but not septic. Some cerumen was removed from the ears, and the membranes found to be thickened and retracted. The Bárány test was positive. The basal metabolic rate was −36 per cent.; the pulse-rate 58, the systolic blood-pressure 110 mm., the diastolic 70 mm., at rest in bed. The patient's weight was 183½ pounds. A diagnosis of typical myxedema was made.

The patient was admitted to the Colonial Hospital August 27th in order that, under uniform conditions, the basal metabolic rate both before and after the intravenous injection of thyroxin might be followed. The morning of August 28th the basal metabolic rate was −42 per cent., the pulse-rate 50, and August 29th the rate was −41 per cent., the pulse-rate 58. The weight was 183¾ pounds. August 29th at 5.00 P. M. 16 mg. of thyroxin were given intravenously. During the night the patient developed the characteristic symptoms of reaction, headache about two hours after the injection, backache about five or six hours later, and pain in the muscles and joints. There was slight nausea, but no vomiting. Fifteen hours after the injection the basal metabolic rate had risen to −28 per cent. and the pulse-rate to 78. At this time the edema had begun to disappear from the face, and the patient appeared brighter and more alert. He said he was less sleepy, was warmer, and could talk better.

September 1st the basal metabolic rate was −13 per cent. and the pulse-rate 78; September 2d the basal metabolic rate was −17 per cent.; the pulse 67; September 3d the basal metabolic rate was −15 per cent. and the pulse 64. The weight was 171 pounds, a loss of 12¾ pounds since August 29th. The patient had improved remarkably, he was more alert, his rate of speech was normal, the voice was less hoarse and thick, and except for weakness and some slight remaining edema, in spite of his marked loss in weight, he felt quite like himself.

September 4th at 4.40 P. M. a second intravenous injection of 8 mg. of thyroxin was given. The next morning the basal metabolic rate was −7 per cent. and the pulse 69. September 6th the rate was −1 per cent. and the pulse 78. After the second injection the subjective reactions were less severe than after the first injection. September 9th the daily dosage of 1.6 mg. of thyroxin was begun and the basal metabolic rate slowly increased from −1 per cent. to +7 per cent. September 19th, with the pulse 84. At this time all the edema was gone. The patient weighed 157 pounds. His facial expression was about normal, no longer showing the typical myxedema facies. His appetite was still poor, but he was beginning to regain his strength. There was marked improvement in his ability to walk. His voice was clear and his speech normal. His skin was warm, somewhat moist, and the scaly skin has been shed almost entirely. He still complained of some sciatic-like pains. He expressed himself very decidedly on his subjective improvement and stated many times that he felt like a different man, "as though he had been born again." September 19th the patient at his own request was allowed to go home, although there was still some uncertainty whether or not the proper daily dosage of thyroxin had yet been established.

The 3 cases briefly detailed will serve as examples of the value of the basal metabolic rate in the diagnosis and treatment of thyroid disorders. We believe that the general use of the basal metabolic rate for the diagnosis and during the course of treatment of disorders of the thyroid gland will advance our knowledge and ability properly to treat these cases in the same way as

the introduction of the thermometer aided in the diagnosis and treatment of febrile disorders.

Case 285377. Dr. L. A.S, aged 55.

Diagnosis: Myxedema

	Basal Metabolic Rate %	Respiratory Quotient	Systolic mm.	Diastolic mm.	Pulse pressure mm.	Pulse	Temperature °F.	Weight kg.
1919								
8/25	-36	0.78	110	70	40	58	98.0	83.2
8/27	Admitted to hospital							
8/28	-42	0.86	120	86	34	50	97.4	83.5
8/29	-41	0.87	116	80	36	58	98.0	82.9
8/29	16 mg. thyroxin intravenously at 5:00 p.m.							
8/30	-28	0.78	108	80	28	78	98.2	81.1
8/30	-28	0.80	116	86	30	73	98.6	81.1
9/1	-13	0.74	118	84	34	78	98.7	77.6
9/2	-17	0.74	128	84	44	67	98.3	77.4
9/3	-15	0.78	142	98	44	64	98.2	77.6
9/4	8 mg. thyroxin intravenously at 4:40 p.m.							
9/5	- 7	0.76	132	86	46	69	98.6	76.2
9/6	- 1	0.82	132	88	44	78	98.6	76.0
9/8	+ 1	0.79	120	82	38	81	98.6	74.8
9/9	1.6 mg. thyroxin daily							
9/10	+ 1	0.75	118	80	38	82	98.2	73.2
9/12	+ 3	0.76	108	76	32	79	97.2	72.3
9/15	+ 5	0.71	120	78	42	80	97.9	71.7
9/17	+ 4	0.81	108	66	42	79	98.0	71.2
9/19	+ 7	0.73	110	72	38	84	98.4	71.3
9/19	The patient was sent home and instructed to take 1.6 mg. thyroxin daily							

THE PREOPERATIVE TREATMENT OF HYPERTHYROIDISM

F. A. WILLIUS, M. D.

MANY patients suffering from exophthalmic goiter (hyperplastic toxic goiter) and from thyroid adenoma (non-hyperplastic toxic goiter) present themselves for examination at a time when operative procedures are inadvisable for various reasons.

The usual operative contraindications are intense hyperthyroidism and damage to the cardiovascular mechanism. Less frequent contraindications are hypertension, nephritis, diabetes mellitus, and acute and chronic respiratory infections.

Much valuable knowledge is gained by observing the patient while ambulatory, and subsequently while at rest. The stress and excitement of the examination period often exaggerates the clinical picture of the disease.

The age factor in hyperthyroidism referable to the extent and degree of visceral damage is important from the standpoint of preoperative management. Exophthalmic goiter occurs in all periods of life, but most frequently in the third and fourth decades. Thyrotoxic adenoma is observed more often in middle and later life, although occasionally younger persons are affected. Marked cardiovascular damage usually means a very intense hyperthyroidism for a relatively short time, or a mild or moderate hyperthyroidism for a long time. It is obvious that the heart muscles of older patients do not tolerate toxic influence so well as those of younger patients. The majority of cases of marked myocardial degeneration is found in middle and later life.

Management of the Patients.—The patients are placed at absolute rest in bed and are not permitted to get up during this period. It is necessary to gain their co-operation in this regard, since physical and mental relaxation are of equal importance.

It should be emphasized in dealing with sufferers with hyperthyroidism that an extremely nervous group of patients is being treated, persons whose nervous irritability is marked, and who become completely upset and very emotional at the least provocation. It is absolutely necessary for all persons in attendance on these patients, from orderly to physician, to exercise tact and diplomacy.

Experience at the Mayo Clinic has taught us to deal frankly with the goiter patients. Deception as to the time of operation or the operative procedure to be followed is never practised, and this has created a wholesome attitude of anticipation rather than an uncertain fear.

Diet.—With the exception of stimulants, such as tea, coffee, and cocoa, a full general diet is allowed except when special contraindications arise, as in nephritis and diabetes mellitus.

Cardiac Therapy.—The treatment of cardiac complications deserves special mention. The cardiac damage is principally myocardial, although the interesting group of patients having pre-existing valvular disease somewhat alters the usual phenomena. In all types of cardiac affections the crucial issue, however, is myocardial integrity.

The use of digitalis is beneficial in most cases, and, as when it is employed in other diseases, three important principles must be remembered: (1) The use of a potent preparation, (2) the administration of sufficiently large doses to obtain the desired action, and (3) rest in bed during the period of administration. Patients having auricular fibrillation respond best to digitalis, although it is erroneous to assume that this drug avails little when the cardiac action is rhythmic.

We have found it advisable in cases with edema to withhold digitalis for from twenty-four to thirty-six hours to permit the action of physiologic rest. The use of the drug, especially its oral administration, must be guarded when nausea and vomiting are present. The rectal administration of digitalis may at times seem advisable in doses of 4 to 6 c.c. of a potent standard tincture in 100 c.c. of normal saline solution, repeated two or three times daily.

The value of preoperative digitalization is repeatedly shown by patients who immediately following surgical procedures present evidence of acute heart failure. It must be recalled that digitalis given orally does not have a definite action for from twenty-four to thirty-six hours. Our experience with hypodermic preparations has not been satisfactory; their administration implies the necessity for immediate action, which, as a rule, it has not been our good fortune to observe. The subsequent administration of digitalis to a digitalized patient is a simple procedure and is often attended by a sense of security on the part of the physician. Intravenous digitalis medication has as yet not been used in the Mayo Clinic.

The Crisis.—The management of the patient during the crisis is important. By crisis in exophthalmic goiter is meant the syndrome attending the period of intense hyperthyroidism and toxicity, characterized by extreme nervousness and restlessness, nausea and vomiting, often diarrhea, rapid loss of weight, and usually rapid and tumultuous cardiac action. Opiates are often necessary and should be employed to permit as much rest as possible, but hypermorphinization should be avoided. If vomiting interferes materially with food intake, unless diarrhea is present, enteroclysis by the drop method is a satisfactory means of introducing fluids. Tap-water or water to which has been added glucose 5 per cent. and sodium bicarbonate 2 per cent. is of value. When the bowel does not tolerate fluids, hypodermoclysis must be resorted to. Operative procedures, even palliatives, such as intraglandular injections of boiling water, or quinin and urea, are hazardous during this period.

Diarrhea.—Frequently intermittent diarrhea is observed, not attending the crisis, and is usually satisfactorily controlled by the administration of powdered opium and calomel, $\frac{1}{4}$ gr. of each, three or four times daily. This has given better results than bismuth. Fruit and high protein foods should be withheld during the period of diarrhea.

Other complications, such as nephritis and diabetes mellitus, demand the usual preoperative care, and will not be discussed here in detail.

The routine administration of sedatives, such as quinin hydrobromid, has been abandoned and is given only as judgment dictates.

Emphasis must be placed on the value of surgical and medical correlation in the preoperative and postoperative management of hyperthyroidism. The factors and the judgment determining the time of operation and the best operative procedures to be employed in a given case are important and interesting subjects, but they cannot be considered in the space accorded this discussion.

A CASE OF CARDIOSPASM WITH DILATATION AND ANGULATION OF THE ESOPHAGUS

P. P. VINSON, M. D.

THIS case is reported not only because of several unusual characteristics but also to emphasize again the value of a silk thread as a guide in esophageal work. With or without gastrostomy the use of this silk thread simplifies very greatly all esophageal instrumentation.

Dunham, in 1903, presented a method of dilating cicatricial stenosis of the esophagus: A silk thread was first swallowed by the patient, after which a gastrostomy was performed; the thread was then brought out through the gastrostomy opening and sounds were passed into the stomach, using the thread as a guide. Six years later Mixter simplified Dunham's technic by having a patient swallow enough silk thread so that it would pass through the stomach into the intestine far enough to permit of its being drawn perfectly taut when dilatation was attempted, thus doing away with the necessity of a gastrostomy. In 1910 Plummer published a description of this method of using the silk thread, but as yet it seems to be used by comparatively few physicians.

CASE REPORT

CASE A281711.—Mrs. H. W., aged forty-five, came to the clinic July 24, 1919, complaining of vomiting, loss of weight and strength, and pain in the stomach.

Following an operation for acute appendicitis two years before coming for examination the patient began to have a dull pain in the pit of the stomach, with belching and vomiting immediately after meals, and a feeling as though the food would stick at the cardia. This condition persisted. The patient

had eaten small meals to prevent vomiting, but in spite of this she at times vomited food in the morning that she had eaten the night before. There was no history of jaundice or of acute abdominal attacks. At times she became very short of breath and felt as if she were smothering. In other respects the history was negative.

Fig. 111.—Case 281711. Cardiospasm with acute dilatation of the esophagus.

A roentgenogram of the esophagus showed a spasm at the cardia, with marked dilatation and kinking of that organ. A diagnosis of cardiospasm with diffuse dilatation of the esophagus was made (Fig. 111).

After the patient had swallowed six yards of twisted buttonhole silk thread dilatation was attempted, but it was found that the acute angulation of the esophagus would not permit of the olives' entering the cardia without breaking the fine

thread. She again swallowed the fine thread, to which a heavier silk thread was attached, and after two days it was found that she had swallowed a sufficient amount of the heavy thread to

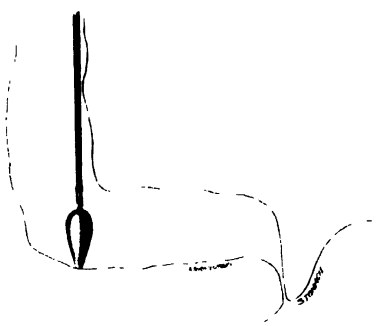


Fig. 112.—Showing the natural inclination of a plain olive passed into the esophagus without the thread as a guide.

permit of the dilatation. After some manipulation a hydrostatic dilator was passed into the cardia, which was dilated up

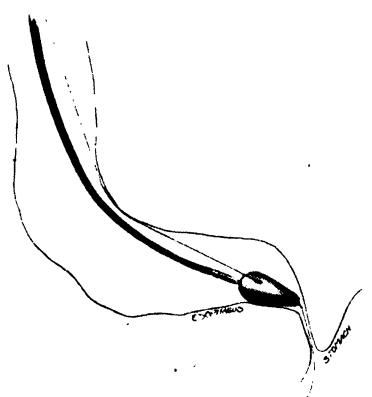


Fig. 113.—Showing a plain olive being passed into the stomach, using the silk thread as a guide.

to 30 feet of water pressure. Very little discomfort accompanied this stretching. A week later the patient was permitted to return home, completely relieved of all her symptoms.

Without the use of the thread as a guide it would have been practically impossible to pass any dilating instrument into the

Fig. 114.—The hydrostatic dilator being passed into the cardia, using the thread as a guide. Ordinarily a plain olive is used on the end of the dilator, but in this case it was found necessary to use the wire spiral.

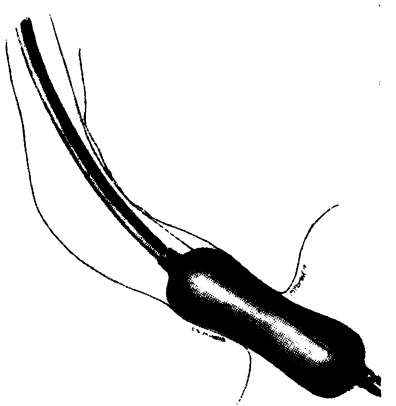


Fig. 115.—Showing the distended hydrostatic dilator in place.

cardia unless a gastrostomy had been performed, and even with a gastrostomy the silk thread would have been a great help in

passing the dilator. An esophagoscopic examination would have been of very little value, and treatment through an esophagoscope would probably have been quite ineffectual. Figures 112–115 illustrate the difficulties that would have been encountered.

Like all other cases of cardiospasm this patient has a 25 per cent. chance of a recurrence of her trouble, but further dilatations should absolutely cure the condition.

BIBLIOGRAPHY

1. Dunham, T.: New Instruments for the Treatment of Esophageal Stricture, Ann. Surg., xxxvii, 350–359, March, 1903.
2. Mixter, S. J.: Symposium on the Surgery of the Esophagus, from the Standpoint of the General Surgeon, Trans. Amer. Laryngol. Assoc., 342–349, 1909.
3. Plummer, H. S.: The Value of a Silk Thread as a Guide in Esophageal Technique, Surg., Gynec., and Obst., x, 519–523, May, 1910.

MEDIASTINAL AFFECTIONS IN CHILDHOOD

W. S. LEMON, M. B.

THE neoplasms and inflammatory tumors of the mediastinum of childhood differ but little in symptoms or signs from those of adult life; there are, however, fewer varieties. In the series I have studied, lymphosarcoma, enlarged thymus, tuberculosis of the tracheobronchial lymph-nodes, and Pott's disease with abscess have been most frequently encountered.

The condition of lymphosarcoma in childhood (Fig. 116) is particularly rare, having been seen but once in the *x*-ray examinations of children's chests at the clinic. The tumor gives the usual pressure symptoms, depending on the size, the rapidity of the growth, and the location within the mediastinum; it may show metastasis within the lung tissue.

The enlarged thymus is, perhaps, the most frequent tumor of the mediastinum found in early infancy. The presence of this enlarged gland, and its association with status lymphaticus, which so frequently results in sudden death, has been extensively discussed. Three such cases have come under my observation; all the patients died. The gland itself did not seem to be markedly enlarged; this would seem sufficient reason to doubt that the size itself is the important factor. Olivier considers all thymuses weighing more than 15 gm. to be hypertrophic; in status lymphaticus the usual weight, according to Kerley, is from 10 to 20 gm., although it may be as high as 55 gm. An enlarged thymus may displace the lobes of the lung on either side, and reach from above downward, so that it overlaps the base of the heart. In the *x*-ray shadow the heart shadow becomes continuous with that of the gland. In the case presented this was found to be true (Fig. 117).

Our interpretation of the presence of persistently enlarged glands at the hilus depends in a large measure on our concep-

tion of tuberculosis of childhood. Two opinions prevail. Norris and Landis and others believe chronic tuberculosis in children to be less frequent than was formerly supposed, that primary lung infection in childhood is found within the nodes, and that invasion of the lung is secondary. Opie, in his paper on focal tuberculosis in children and adults, asserts that pulmonary

Fig. 116.—Case 127428. M. D., a girl aged four. Hoarse voice; croupy cough with bloody sputum; dyspnea; coarse râles; tumor of mediastinum; lues hereditaria. Necropsy findings: Lymphosarcoma.

tuberculosis in infancy and early childhood is primary, and is accompanied by enlargement and by cessation of both the intrapulmonary bronchial lymph-nodes and the tracheal lymph-nodes. He points out that the lesion may not be in the apices of the lung, but rather has a tendency to frequent the middle part of each lung, especially the middle lobe of the right and the corresponding portion of the left, that cavities are a rare accom-

paniment, and that there is very little tendency to the formation of fibrous tissue, but a frequent tendency toward dissemination into the meninges, spleen, and other organs.

It is known, of course, that the apices and the second intraspaces in adults are usually affected first in pulmonary tuberculosis, that fibrous tissue and cavity formation is frequent, and

Fig. 117.—Case 290922. B. G. M., a girl aged four months. Angioma of the left labium. Tentative diagnosis of malignant tumor. *x*-Ray for metastasis showed enlarged thymus, but no metastasis.

that the lymphatic nodes are not markedly involved. Except in acute miliary tuberculosis the meninges, spleen, and other organs are either not involved at all or they are involved late in the disease. Ghon, like Opie, believes that the lung involvement is primary and that the gland involvement is secondary; he quotes a series of 19 cases in which tuberculosis of the lung

was associated with glandular lesions; the gland was affected in only one case in which the lung lesion was not discovered. Holt, on the other hand, quotes Northrop and Bollinger as having found at necropsy tuberculous glands in children who had died of acute diseases other than tuberculosis. Loomis experimentally produced tuberculosis in animals by inoculation from the glands of persons dying of diseases other than tuberculosis who had showed no previous evidence of tuberculosis.

Fig. 118.—Case 286831. B. S., a boy aged five. Ill with fever, temperature 99° to 101° F.; slow recovery; persistent teasing cough, and vomiting with cough. Pleurisy; tired and listless; asthmatic breathing; laryngeal stridor; emphysema. Large tonsils and adenoids. Tuberculosis.

If the child is not very young, or, in other words, is from three to ten, the disease in the gland may resolve and the child become healthy. If the gland fails to resolve, cessation and ulceration occurs and the lung becomes invaded. The glands may become very large and, because of their location at the hilus, may cause any one of the pressure symptoms that are

common to other inflammatory conditions or neoplasms in this area. In one of these cases the child showed every evidence of emphysema, and had a teasing cough which resembled that of asthma, but was persistent rather than paroxysmal (Fig. 118). The cough may resemble pertussis without the whoop, or it

Fig. 119.—Case 225360. T. D., a boy aged six. Dactylitis of first phalanx of third left finger and first phalanx of great toe; kyphosis; pain in joints of spine; child supported himself with hands on hips; marked improvement followed application of brace. Pott's disease.

may be paroxysmal and resemble croup. The glands were of such size as to form a mediastinal tumor and to be demonstrable on physical examination, giving evidence of a broadened mediastinal dulness. D'Espine's sign was negative. I have not seen any cases in which a mediastinal abscess has presented anteriorly in the suprasternal notch or posteriorly to simulate Pott's dis-

ease. The mediastinal mass is bilateral and feathery, occurring at the hilus, and typical of inflammatory affections of this area.

Pott's disease with abscess in the posterior mediastinum has been found in several cases observed in the clinic. Signs of tuberculosis usually exist elsewhere in the body. In the case shown (Fig. 119) the presence of dactylitis and kyphosis, a rigid spine, and abdominal pain indicated the necessity of an *x*-ray examination. In the plate a dense shadow was discovered superimposed on the spine. Evidence of a narrowing of the costal angles and accompanying damage to the dorsal vertebræ was also found.

Besides the cases of mediastinal tumors in which a positive diagnosis is possible are those in which a definite opinion cannot be given. Usually such patients present themselves for examination because of pressure symptoms and signs. The physical examination may not offer any explanation, and only *x*-ray examination of the chest may reveal the cause, but not its nature.

BIBLIOGRAPHY

1. Bollinger: Quoted by Holt.
2. Ghon, A.: The Primary Lung Focus of Tuberculosis in Children, Eng. ed. authorized translation, by D. B. King, New York, Hoeber, 172 pp., 1916.
3. Holt, L. E.: The Diseases of Infancy and Childhood, New York, Appleton, 1136 pp., 1903.
4. Kerley, C. G.: The Practice of Pediatrics, Philadelphia, Saunders, 878 pp., 1914.
5. Loomis, H. P.: Some Facts in the Etiology of Tuberculosis Evidenced by 30 Autopsies and Experiments Upon Animals, Med. Rec., xxxviii, 689–698, December 20, 1890.
6. Norris, G. W., and Landis, H. R.: Diseases of the Chest and the Principles of Physical Diagnosis, Philadelphia, Saunders, 728 pp., 1918.
7. Northrup, W. P.: Tuberculosis in Children. Primary Infection in Bronchial Lymph-nodes, with Exhibition of Illustrative Specimens, New York Med. Jour., liii, 201–205, February 21, 1891. Quoted by Holt.
8. Olivier: Quoted by Kerley.
9. Opie, E. L.: The Focal Pulmonary Tuberculosis of Children and Adults, Jour. Exper. Med., xxv, 855–876, June, 1917.

DIFFERENTIAL DIAGNOSIS OF MEDIASTINAL AFFECTIONS

W. S. LEMON, M. B.

IN few parts of the body is there a greater number of important structures confined in so small an area than in the mediastinum. Because of this fact a knowledge of anatomic relationships is most necessary in making a study of the diseases and neoplasms that affect this part. For convenience the mediastinum may be considered as divided into three parts—the anterior, middle, and posterior. This classification has been adopted since roentgenology has begun to give important assistance to the clinician in the study of mediastinal disease. The three parts are as follows:

1. Anterior:
   - (*a*) Remains of the thymus or the thymus itself.
   - (*b*) Lymph-nodes.
   - (*c*) Areolar tissue.

2. Middle:
   - (*a*) Heart with its arterial and venous trunks.
   - (*b*) Trachea and bronchi.
   - (*c*) Hilus of lung on each side.

3. Posterior:
   - (*a*) Lymph-nodes.
   - (*b*) Esophagus.
   - (*c*) Thoracic duct.
   - (*d*) Vagus, phrenic, and sympathetic nerves.

A certain group of symptoms is common to diseases affecting the mediastinum, that is, symptoms of pressure on its several structures. The following tabulation of these symptoms is based on a summary used by Blair, and further developed from experience in my own series of 37 cases (Table 1).

Table 1

COMMON PRESSURE SYMPTOMS AND SIGNS

1. Esophagus	Dysphagia (a) persistent when due to direct pressure (b) transient when due to irritation of the recurrent laryngeal nerve
2. Trachea	Brazen cough (gander cough) Dyspnea - often only on exertion Stridor with bellows breathing and indrawn manubrium sterni Bronchorrhea Hemoptysis
3. Root of lung and pleura	Difficult and insufficient aeration like phthisis Pulmonary collapse, consolidation or chronic pneumonia May vary from time to time with variation in pressure
4. Nerve trunks	Neuralgic type of pain. Paroxysmal and intermittent
5. Pulmonary artery	Systolic murmur, dilated right heart
6. Superior vena cava	Cyanosis - edema of head and neck and upper extremities Collateral do not pulsate as in cardiac disease
7. Right pulmonary veins	Hydrothorax and collapse of lung
8. Thoracic duct	Marasmus
9. Cardiac plexus	Anginal attacks - simulating angina pectoris 3rd cervical to 3rd dorsal segmental distribution
10. Sympathetic nerves	Dilated pupils, indicating irritation Contracted pupils, indicating paralysis No loss of reflex except in lues Unilateral sweating, flushing or pallor
11. Vagus nerves	Dyspepsia, nausea, vomiting, dyspnea, hiccough
12. Recurrent laryngeal nerves	Hoarseness, aphonia, spasm or paralysis of the left vocal cord - suffocation
13. Right recurrent laryngeal nerves	Right-cord paralysis
14. Phrenic nerves	Unilateral paralysis of the diaphragm. Pain about the neck just above the clavicle

The organs and lesions studied in this series of cases are as follows:

1. Benign neoplasms.
2. Malignant neoplasms.
3. Abnormally placed organs:
   (*a*) Substernal goiter.
   (*b*) Thymus.
4. Hodgkin's disease.
5. Lymphosarcoma.
6. Tuberculosis.
7. Pathologic conditions in the circulatory system:
   (*a*) Aortitis.
   (*b*) Dilatation of the aorta from pressure.
   (*c*) Mitral stenosis.
   (*d*) Cardiac hypertrophy, especially with aortic insufficiency.
   (*e*) Pericarditis with effusion.
8. Pott's disease.
9. Aneurysm of the thoracic aorta.
10. Syphilis:
    (*a*) Gumma.
    (*b*) Syphilitic mediastinitis.

Benign Neoplasms.—Benign tumors of the mediastinum are interesting to the pathologist, but are not of great importance to the clinician because of their rarity. Early this year I reported a case of intrathoracic chondroma which originated in the second rib.[5] The history and the pathologic and the roentgenographic findings established the character of the growth so plainly that there was no difficulty in identifying it (Fig. 120). Parham and Beck, who have reported similar growths in the mediastinum, assert that they usually invade this area from the chest wall. W. J. Mayo has observed 2 cases of dermoid cyst which were diagnosed by the finding of bits of hair and teeth in the sputum. Dr. Brown, at Trudeau Sanitorium, has also observed 1 case (Fig. 121). I have seen only 1 case of actinomycosis of the lung; this was thought to be tuberculosis until a skin lesion on the chest wall made the diagnosis apparent (Fig. 122).

Malignant Neoplasms.—Malignant growths in the mediastinum present the same general characteristics as elsewhere in the body. Carcinoma which mainly affects patients in middle life grows rapidly, develops pressure symptoms early, and usually causes death within six months. Effusion of blood, or

blood-stained fluid, is frequently found in the pleural space. In 2 cases which came to my attention glands almost as hard as stone were present in the supraclavicular area; in one of these diagnosis was established on excision and microscopic examination. Malignant tumors are usually single, they vary in size, and show a distinct outline on *x*-ray examination (Fig. 123).

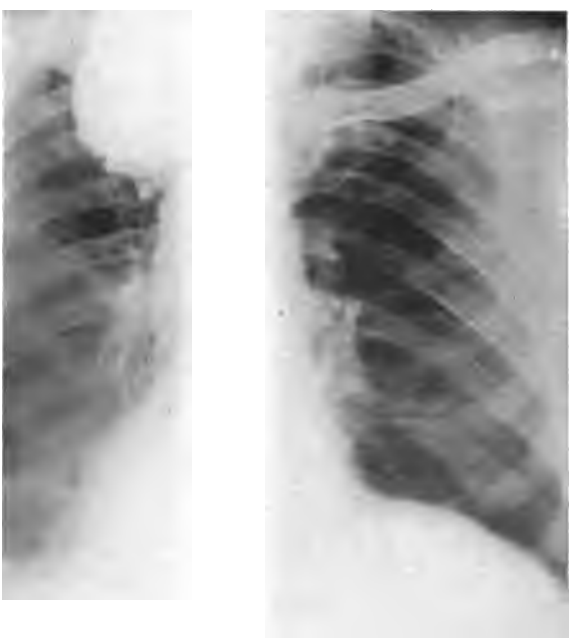


Fig. 120.—Case 188051. Chondroma. Clinical findings: Pressure. *x*-Ray shadow: Superficial, unilateral, clearly circumscribed, calcified.

They may be infiltrating in type and grow outward into the thorax from the hilus. The miliary type, which closely resembles miliary tuberculosis, does not involve the mediastinum itself. One of our recent cases was diagnosed by microscopic examination of a supraclavicular gland. These patients may, of course, present any of the symptoms outlined in Table 1.

Abnormally Placed Organs.—(*a*) Substernal goiter may exist

for years without symptoms, although it usually manifests itself by dyspnea or hoarseness due to pressure on the trachea, bronchi, or the recurrent laryngeal as it passes upward between the trachea and esophagus. The width of the mediastinal dulness is increased, and, as is common with mediastinal conditions, an increased bronchial type of breathing is heard on auscultation. The diagnosis presented difficulty in only one case in this series.

Fig. 121.—Brown's case. Dermoid cyst. Clinical findings: Pressure; hair in sputum. *x*-Ray shadow: Unilateral and clearly circumscribed. Teeth in shadow. (*x*-Ray plate reproduced by courtesy of Dr. Vinson.)

x-Ray examination reveals a tumor well defined and continuous with the extrathoracic or cervical shadow (Fig. 124). (*b*) In children the *x*-ray shadow of the thymus resembles that of the substernal goiter. It is centrally located, continuous from above downward, and frequently is superimposed on the heart shadow. It is the most frequent mediastinal tumor of infancy.

Hodgkin's Disease.—Usually Hodgkin's disease can be dif-

ferentiated readily. In each case in this series some factor made the diagnosis certain before the condition of the chest was analyzed. Glandular enlargement elsewhere afforded an oppor-

Fig. 122.—Case 130341. Actinomycosis. Clinical symptoms resembling tuberculosis. Sulphur bodies in sputum. Penetration of chest wall. *x*-Ray shadow: Fimbriated halo indicative of inflammatory conditions.

tunity of making a microscopic examination. The general health of the patient, temperature, anemia, malaise, weakness and anorexia, the enlarged liver, and splenomegaly present evidence which makes a correct diagnosis reasonably certain. The

mediastinal growth extends from the hilus, is bilateral, diffuse, and "feathery" in appearance; frequently there is evidence of fluid in the pleural space (Fig. 125). In leukemia the blood-picture presents positive evidence in the diagnosis.

Lymphosarcoma.—This is the most common of mediastinal neoplasms and one of the few conditions which is confused with

Fig. 123.—Case 248656. Malignant tumor. Clinical symptoms: Extreme grade pressure. Bloody serum drained seven times without relief of dyspnea. Death from suffocation after six months. *x*-Ray shadow: Unilateral and circumscribed after aspiration.

Hodgkin's disease. The tumor is readily found by percussion, and on *x*-ray examination usually appears unilateral and distinctly circumscribed. Frequently metastasis is present. If the tumor is in the area occupied by the aorta and has taken on referred pulsation, the roentgenologist may encounter difficulties.

Fig. 124.—Case [illegible] Posterior group. Clinical symptoms: Pressure. *x*-Ray shadow extended from above downward. Displacement of trachea.

crackling râles on auscultation were very marked. The two conditions present many points of similarity, but the fever, the tuberculosis bacilli in the sputum, and the course of the disease should make the diagnosis positive even without the assistance of a fluoroscopic examination. A cavity placed so that it receives referred pulsation may cause some confusion, but usually it occurs in cases that are otherwise easily recognized as tuberculosis.

Pathologic Conditions in the Circulatory System.—(*a*) Aortitis may be recognized by the presence of Potain's sign, the increase in substernal dulness, the "clanging" character of the second aortic sound, and the possible presence of a systolic or diastolic murmur when the ring is affected. Unlike aneurysm,

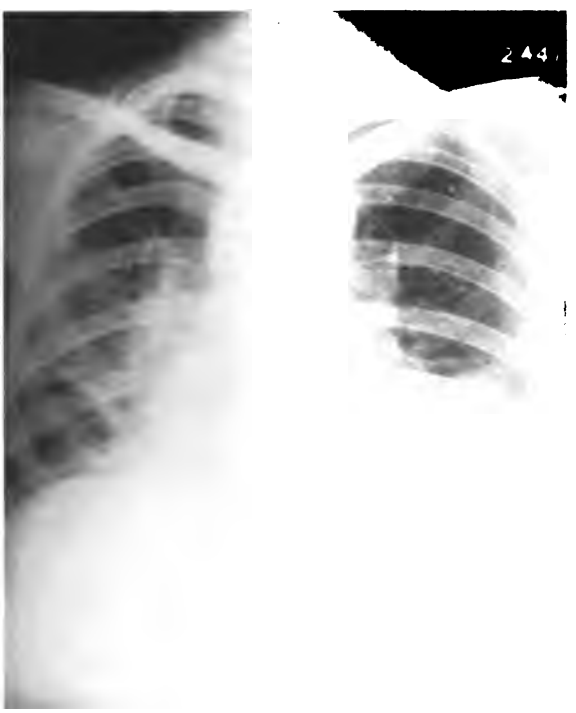


Fig. 125.—Case 244179. Hodgkin's disease. Clinical findings: Adenopathy; splenomegaly; general disability; fever; emaciation; edema. Gland removed for microscopic examination. *x*-Ray shadow: Bilateral, symmetric feathery shadow of effusion at each hilus.

the systolic element predominates. Pain is substernal and resembles that of angina pectoris, but evidence of arteriosclerosis, increased blood-pressure, and recurring attacks which characterize angina pectoris are lacking. Like angina, however, the pain of aortitis is increased by exercise. It is distinguished with difficulty from early aneurysm of the aorta at the area of Val-

salva. Very often the fluoroscope and plate decide the diagnosis (Fig. 127).

(*b*) Dilatation of the aorta from high pressure, appearing usually in the aged, especially when associated with cardiac hypertrophy, offers no diagnostic difficulties after the completion

Fig. 126.—Case 131482. Lymphosarcoma. Clinical symptoms not always distinguishable from those of Hodgkin's disease. Gland removed for microscopic examination. *x*-Ray shadow: Unilateral, distinctly circumscribed. Metastasis.

of the clinical and *x*-ray examinations of the case. In the case illustrated the blood-pressure readings were systolic 240, and diastolic 140. There were no symptoms referable to the aortic enlargement. The substernal area of dulness was markedly broad, reaching a width of 9 cm.

(*c*) Mitral stenosis may be confused with mediastinal affec-

tions, especially aneurysm, because the backward pressure may be sufficient to cause a lack of synchrony between the two pulses and a variation in their respective pressure readings. This has been explained by assuming that the pulmonary artery becomes enlarged and wedged beneath the aortic arch at the point of origin of the left subclavian, and by consequent interference with

Fig. 127.—Case 251358. Aortitis. Clinical findings: Potain's sign; to-and-fro murmur, systolic predominance; aortic second sound clanging or reverberating; substernal pain. *x*-Ray shadow: Uniformly broadened.

the blood flow causes the pulse variability and pressure discrepancy. By pressure on the recurrent laryngeal paralytic symptoms may be produced in the larynx.

(*d*) Simple cardiac hypertrophy can be distinguished from pericarditis with effusion by the character of the heart sounds. They are clearly heard, are characteristic of the particular lesion

present, and serve to indicate the extent of cardiac decompensation. The *x*-ray shadow is that of a normal heart, much magnified. The heart with effusion presents sounds indistinctly heard, frequently without indication of a specific lesion or of cardiac decompensation. The *x*-ray shadow is pear shaped, filling the

Fig. 128.—Case 246651. Pott's disease. Clinical findings: Neuralgic pain; rigidity of spine; kyphus; evidence of tuberculosis elsewhere; dactylitis; bronchitis; dulness and absence of systolic sounds in interscapular area. *x*-Ray shadow: Fusiform, symmetric, superimposed on spine, with accompanying destruction of vertebræ. Narrowed costal angles.

costohepatic angle, and uniformly continuous over the auricular and ventricular areas. "Because of the strong cardiac impulse and intensity of the heart sounds simple hypertrophy of the heart should cause no confusion."[7]

(*e*) Norris and Landis state concerning pericardial effusion:

"A tumor involving the anterior mediastinum at times assumes the pyramidal shape of a pericardial effusion. In case of an effusion the cardiac symptoms are usually marked while pressure symptoms are absent; the reverse is true in cases of tumor. As in all mediastinal affections, the *x*-rays are invaluable."

Pott's Disease.—Two cases of Pott's disease were studied in the series. A child with mediastinal disease is primarily suspected of having Pott's disease with abscess or tuberculosis of the tracheobronchial lymph-glands. *x*-Ray examination shows a fusiform symmetric shadow superimposed on the spine with destruction of the vertebræ and a narrowing of the costal angles (Fig. 128). The gait, the rigid and tender spine, the resulting kyphosis, and the character of pain are sufficient to establish a diagnosis.

Aneurysm usually appears in young adults, especially in vigorous males, in whom a history of syphilis, positive clinical findings, or a positive Wassermann is obtained in 85 per cent. of all cases. Pain, which is present in almost all cases, is anginoid in character when the orifices of the coronaries are affected; it is vague and not severe when aneurysm is quiescent, gnawing and boring when the vertebræ are eroded. Any of the pressure symptoms may be present, especially when the transverse portion is affected, in which case dysphagia, dyspnea, and the so-called brassy cough are most common (Table 1). Aneurysm is the only affection of the mediastinum, other, possibly, than mitral stenosis, that gives evidence of alteration in the pulse-wave, or alteration in the blood-pressure readings on both sides. It presents a localized pulsation, expansile in character, which when seen in the back of the chest is almost certainly diagnostic. Diastolic shock is imparted to the palpating hand and Oliver's sign is sometimes found to be positive. Increased dulness is usually found either in front or behind, depending on the location of the aneurysm, and on auscultation an exaggerated second sound is heard at a distance from the aortic cartilage, the greater the distance, the more significant. Aneurysm is the only tumor that erodes and penetrates the chest wall. "The history of syphilis, attacks of pain like angina pectoris, pulsation of the

dull area, systolic thrill and murmur, diastolic shock, and aortic regurgitation speak for aneurysm."[2] The *x*-ray examination reveals a pulsating tumor directly in association with the circulatory mechanism (Fig. 129).

Fig. 129.—Case 241555. Aneurysm. Clinical findings: Anginal and boring pain; pressure symptoms; positive history of lues and positive Wassermann; expansile pulsating tumor; diastolic shock; exaggerated aortic second sound, diastolic predominance. *x*-Ray shadow of pulsating expansile tumor, associated with circulatory mechanism.

Syphilis.— Gummata show preference for the parenchyma of the lung, but may be found in the mediastinum. Here they are characterized by their chronicity and the rarity of symptoms even though they are of great size. In a few cases gummata of the mediastinum may accompany syphilis of the lung. This occurred in one of our cases and could be demonstrated readily

by the *x*-ray. The usual pressure signs reveal their presence clinically. The history and serologic examination confirm the finding, and their favorable response to therapeutic measures establishes the diagnosis (Fig. 130).

Fig. 130.—Case 242516, 180154. Syphilis. Clinical findings: Very large tumor of long standing; few symptoms other than those from pressure. History of infection and positive Wassermann. *x*-Ray shadow: Large unilateral and well circumscribed; frequently in lung parenchyma. Decreases in size under syphilitic treatment.

(*b*) One other condition remains to be considered, namely, syphilitic mediastinitis. Acute inflammatory mediastinitis and abscess are so intimately associated with other acute infections that they hardly call for differentiation. I have seen but one case of syphilitic mediastinitis and that too recently to include it in this series of cases, which was observed during 1918. Giffin,

however, has described 5 cases. He says: "From a pathologic standpoint, therefore, very little is known concerning this condition, and our diagnoses are not absolute. However, the clinical and therapeutic tests are probably sufficient evidence for a positive diagnosis. In other words, if a chronic diffuse medias-

Fig. 131.—Case 24759. Syphilitic mediastinitis. Clinical findings: Diffuse broadening of substernal dulness; positive history of syphilis and positive Wassermann. *x*-Ray shadow: Diffuse, substernal, lessening under antisyphilitic treatment.

tinal shadow has been demonstrated on radiologic examination, if the Wassermann test shows a very strong positive reaction, and if improvement in the patient's symptoms follows specific treatment, there can certainly be little doubt as to the diagnosis even in the absence of pathologic evidence" (Fig. 131).

BIBLIOGRAPHY

1. Beck, C.: Surgical Diseases of the Chest, Philadelphia, Blakiston, 371 pp., 1907.
2. Blair, A. McN.: The Differential Diagnosis of Mediastinal Conditions, Amer. Jour. Med. Sci., cliv, 240–251, August, 1917.
3. Brown, L.: Dermoid of the Mediastinum. Paper presented before the New York State Med. Soc., October, 1915.
4. Giffin, H. Z.: Luetic Mediastinitis, Jour.-Lancet, xxxiv, 183–185, April, 1, 1914.
5. Lemon, W. S.: Chondroma of the Thorax, Jour.-Lancet, xxxix, 59–60, February 1, 1919.
6. Mayo, W. J.: Personal communication.
7. Norris, G. W., and Landis, H. R. M.: Diseases of the Chest and the Principles of Physical Diagnosis, Philadelphia, Saunders, 728 pp., 1918.
8. Parham, F. W.: Thoracic Resection for Tumors Growing from the Bony Wall of the Chest, New Orleans, 147 pp., 1899.

MYOCARDIAL DISEASE WITH REFERENCE TO THE SUBENDOCARDIAL MYOCARDIUM

F. A. WILLIUS, M. D.

THE term "chronic myocarditis" has been used rather vaguely to denote affections of the myocardium. To reserve the term "chronic myocarditis" for those conditions which are truly inflammatory seems logical. Involvement of the myocardium resulting from degenerative agents and from circulatory disturbances are correctly grouped under myocardial disease.

Much recent knowledge of heart disease has been attained by the use of such methods as electrocardiography. This instrument is practical only in institutions and where "group" medicine is practised, however, and unless this advance in cardiology is applied clinically, it is lost to the profession. My object here is to present in a practical manner a condition the recognition of which was first determined by the electrocardiograph.

A brief consideration of certain anatomic and physiologic facts will aid in clarifying the different phases of the disease (Figs. 132, 133). The rhythmic cardiac impulse originates in a small collection of specialized tissue, the sino-auricular node or cardiac "pacemaker," located in the sulcus terminalis at the juncture of the superior vena cava and the right auricular appendage. From this structure the impulse is diffused through the auricular musculature to reach the first relay station, the auriculoventricular node. This node is found in the right lateral aspect of the auricular septum, just posterior to the septal cusp of the tricuspid valve. The auriculoventricular bundle takes its origin from the anterior extremity of this node, passes downward and backward, and at the level of the membranous septum divides into a right and a left branch. These main

branches pass downward; they divide and subdivide into progressively smaller branches which intercommunicate. They spread out in a fan-like manner in the subendocardial tissue of both ventricles, ultimately coalescing with the individual muscle bundles.

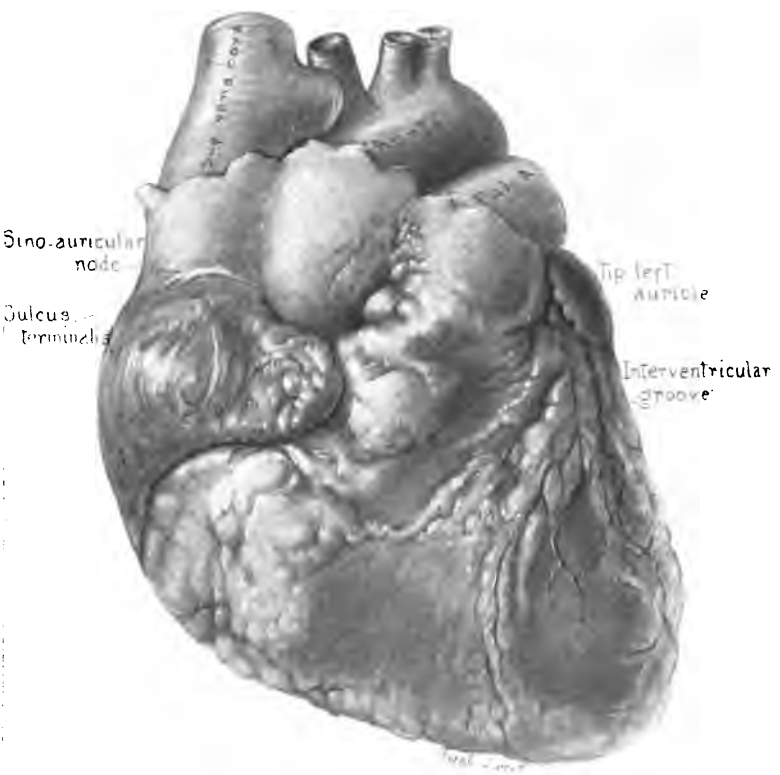


Fig. 132.—Heart, anterior view slightly from right. Location of sino-auricular node. Location of junctional and ventricular conduction system.

The cardiac impulse thus has a definite path from its point of origin to its ultimate destination in the ventricular musculature. The ventricular conduction system has been termed, by virtue of its progressive ramification, the "arborization system."

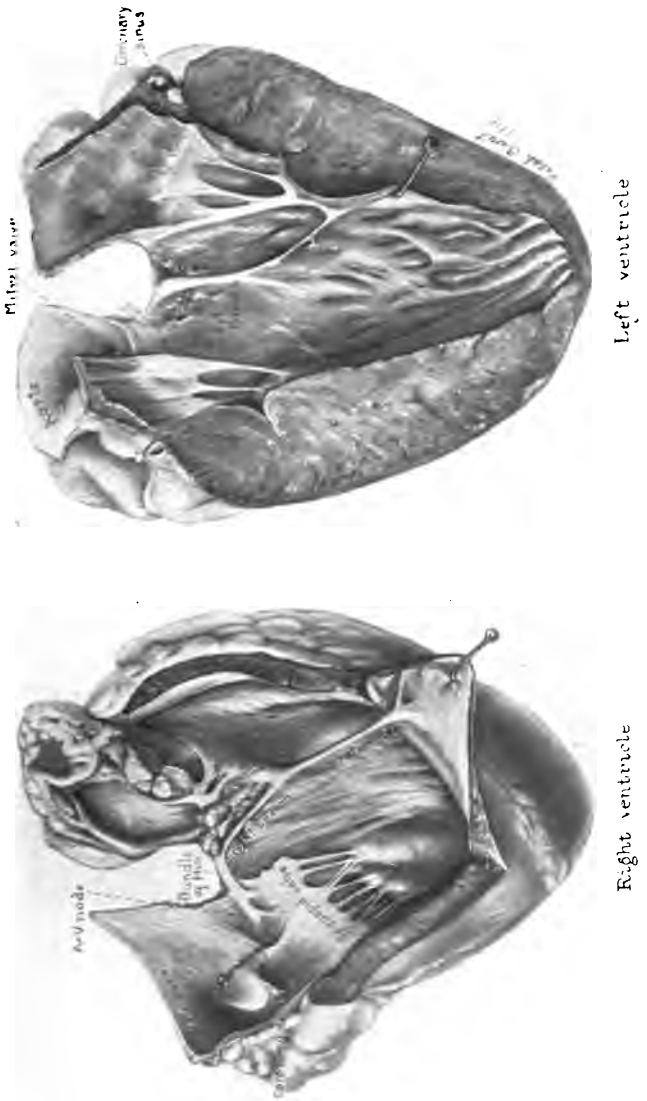


Fig. 133.—Right ventricle and left ventricle.

As previously stated, the arborization system occupies the subendocardial portion of the myocardium; it is the disease of this tissue that I wish to emphasize particularly. It must be

understood that the disease process has no such localizing accuracy as to involve the subendocardial structures alone, but when they are included by the pathologic process quite a definite clinical picture results.

"Arborization block" or "impaired intraventricular conduction" are terms which have been applied to this condition, but as they suggest technical procedures I shall use the term "subendocardial myocardial disease" for practical reasons.

Etiology.—Infection is the most frequent etiologic process in subendocardial myocardial disease, and is present in about half the cases; in the majority of these it is concomitant with or secondary to invasion of the endocardium. Rosenow and Coombs have shown that the infection is embolic, gaining entrance through vascular channels and lodging in a bizzare manner, involving the various cardiac structures, as the case may be. Recalling to mind the intrinsic blood-supply of the heart, it is obvious how a single tissue or all tissues may be damaged simultaneously.

Degenerative processes occur next in order of frequency in about 40 per cent. of cases. They comprise the hypertension group with and without clinical nephritis, thyrotoxic adenomas (non-hyperplastic toxic goiter), and exophthalmic goiter (hyperplastic toxic goiter).

The degenerative process occurring in the hypertension group involves probably three factors: (1) The cause or causes primarily responsible for the constitutional disorder, (2) the action on the myocardium of the retention products or of the intermediate products of incomplete metabolism as toxic agents, resulting from imperfect renal or tissue function, and (3) the increased cardiac stress, affecting largely the myocardium, resulting from the hypertension *per se* and the alterations in cardiovascular balance.

In thyrotoxic adenomas and exophthalmic goiter the noxious agent is a definite chemical substance, thyroxin, shown by Kendall to be the active thyroid constituent. Its action on the myocardium, as on other tissues, is cellular.

Local nutritional disturbances occur less frequently as

etiologic factors in about 10 per cent. of cases. By local nutritional disturbances is meant interference with the blood-supply of the heart. This may occur either by sclerotic and obliterative processes involving the main coronary arteries or their larger branches, or by capillary fibrosis of the terminal vessels, locally or diffusely.

Syphilis appears to play a minor rôle in this disorder; only 5 cases have been observed, and 3 patients had aortic disease with dominant involvement of the aortic endocardium.

Pathology.—Few cases of subendocardial myocardial disease have come to necropsy, but in those hearts which have been examined degenerations of the ventricles were the dominant findings. Fatty and fibrous changes occurred quite constantly.

Symptomatology.—A detailed analysis of the cardinal symptoms of heart failure seems irrelevant. It is sufficient to say that they are the result of the incapacity of the myocardium to perform its function. To emphasize the gravity of subendocardial myocardial disease: The disorder is one affecting the muscle of the ventricles and one of their most important constituents—the conduction system. That life is dependent on ventricular and not on auricular function is clearly detected in auricular fibrillation, a disorder in which the auricles no longer contract; the walls of the auricles are dilated in diastole and the individual muscle bundles are undergoing inco-ordinated fibrillary twitchings.

The degree and extent of muscle involvement directly determine the symptomatology. Instead of dwelling at length on symptoms generally found in heart muscle disease I prefer to emphasize the subjective complaints dominant in this condition. Dyspnea following exertion is constantly observed, but orthopnea and paroxysmal dyspnea, the latter occurring when the patient is at rest, are striking symptoms.

The infrequency of pitting edema is worthy of mention. Patients having subendocardial myocardial disease are up and about with relative comfort even after the disease is quite well advanced. Sudden deaths are infrequent, but when the disease process has reached the stage at which the ventricles are pre-

vented from maintaining a relatively efficient circulation the subsequent progression to a fatal issue is short.

Objective Cardiac Findings.—Auscultatory findings in these cases are very characteristic. The heart sounds are distant and the normal differentiation between the first and second tone is lost. They are often well described as "blanketed" heart sounds.

Differential Diagnosis.—The condition which probably most closely simulates subendocardial myocardial disease is disease of the heart muscle resulting from coronary sclerosis without involvement of the ventricular conduction system. This group does not include angina pectoris, but those cases in which paroxysmal dyspnea is a prominent symptom. Auscultation, as a rule, aids in separating these types, the heart sounds maintaining intensity differentiation when the arborization system is not involved.

The absolute diagnosis of subendocardial myocardial disease is made by the electrocardiograph, although its identification clinically is quite accurate. The electrocardiogram reveals definite abnormalities in the ventricular complex Q R S^s, resulting from delay of the cardiac impulse through normal channels or its passage along circuitous and aberrant conduction paths. The presence of these abnormal complexes in isolated derivations of the electrocardiogram probably indicates localized lesions, while their presence in all three derivations suggest diffuse ventricular changes.

Prognosis.—Subendocardial myocardial disease is a grave disorder entailing a large and early mortality. It should be emphasized that the disease is progressive. In a previous study of 138 cases it was found that 69.6 per cent. of the patients had died in an average of eight and one-half months from the time of examination. The prognosis must, therefore, be guarded at all times.

Treatment.—The elimination of causative agents is of primary importance in the treatment of the disease. The removal of diseased tonsils and teeth with evidence of apical infections must be carefully considered in each instance; this pertains particularly to those cases in which there is an infectious etiology.

When hyperthyroidism exists, thyroidectomy should be performed if the cardiac condition warrants surgery or if the heart can be sufficiently improved by rest and treatment to permit operation.

Those cases secondary to hypertension with and without clinical nephritis should, in addition to cardiac measures, receive treatment for the general condition.

Probably the most important factor in the treatment is the general management of the patient. It is necessary, as in all cardiac affections, to adjust the individual's life to his condition, and especially to limit his activities.

The use of digitalis is of distinct value. Three important principles must be recognized: (1) The use of a potent preparation, (2) sufficiently large doses to obtain the desired action, and (3) physiologic rest during the period of administration. The response to digitalis administered to the patient when at absolute rest in bed strikingly overshadows that obtained in ambulatory patients. Inadequate dosage of the drug largely accounts for the failure in results. The erroneous ideas regarding dosage found in old text-books are probably responsible for the timidity with which physicians in general prescribe digitalis.

BIBLIOGRAPHY

1. Kendall, E. C.: The Active Constituent of the Thyroid, its Isolation, Chemical Nature, and Physiologic Action. Collected Papers of the Mayo Clinic, viii, 513–527, 1916.
2. Rosenow, E. C., and Coombs, C.: The Myocardial Lesions of Rabbits Inoculated with Streptococcus Viridans, Lancet, ii, 1692, 1693, 1913.
3. Willius, F. A.: Arborization Block, Arch. Int. Med., xxiii, 431–440, 1919.

DIETARY INSTRUCTIONS

D. M. BERKMAN, M. D.

I HAVE previously analyzed the reasons for the faulty treatment of diabetes; briefly, they may be summed up as follows: 41 per cent. of the cases remained unrecognized for varying lengths of time; in 17 per cent. the physician made no effort to combat the disease, although in some instances medicine was prescribed; 21 per cent. of the patients had practically discontinued to follow the dietary directions given them by their physicians, and the remaining 21 per cent. were still making conscientious efforts to obey instructions, although working more or less blindly and under conditions evidently greatly changed from those in which the original diets had been prescribed.

In this long-recognized and much-studied disease the perpetuation of the benefit from treatment depends almost wholly on the sustained and intelligent co-operation of patient and physician. Literature, which has recently been enriched largely through the contributions by Allen and Joslin, may acquaint the physician with the most modern and scientific methods of diabetic treatment. It may thus be assumed that for the relatively short time the patient is under the personal care and management of his physician he is receiving accurate attention. After the patient's condition is discovered, however, barely 5 per cent. of the time which remains to him is spent under the immediate direction of a doctor. Unfortunately, each day carries with it the same potential menace of increase in the severity of the patient's condition. Without spending less effort on that 5 per cent. of time in which the physician is directly concerned the other 95 per cent. should be made more profitable. There are two distinct phases in the treatment of diabetes: first, the establishment of tolerance, the estimation of a diet correct for the individual; second, the living up to this diet or its subsequent

alterations. It is this second phase which I wish now to consider.

Efforts should be directed particularly toward treating the patient with average intelligence and education, the average amount of time to devote to his condition, and the average amount of means with which to finance this radical readjustment of his scheme of living. For each individual there is a separate avenue of approach; his co-operation may always be secured by leading him from the maze of elaborate and intricate tables of food values, with bewildering allusions to calories, grams, etc. His education should first consist only of those basic principles which it is possible for him to grasp; then gradually facts of lesser importance may be added as he shows the ability to assimilate them. In short, place in his hands a strong, simple tool with which he can work rather than giving him a complex mechanism which he is sure to discard or abuse through sheer ignorance. The average man who finds that it is necessary to spend six hours or more out of the twenty-four in the care of his condition will after three months decide to take his chances untreated.

For accuracy, while the tolerance is being established, it is wisest to hospitalize the patient if possible. A trained dietitian is almost an essential if many cases are to be handled. Care and patience should be exercised during this period to acquaint the patient with exactly what is being attempted. He should be taught the three food constituents and those groups of food in which they are largely contained. He should be made to realize that by keeping his urine free from sugar the ability of his body to utilize carbohydrates will tend to increase, and vice versa. Finally, he should be given a diet computed by weights of foods; to this should be added a simple table of the ordinary types of food and their values, with an explanation of the arithmetic problem concerned in making any substitutions in his original diet. Reasonable accuracy is desirable in the tables and directions, but fractions and decimals should be used as little as possible. The fact that foods of approximately the same value may be grouped adds greatly to the simplicity.

The simplified and relatively accurate tables and their explanation are intended solely for the use of patients. The food values are taken largely from Joslin's tables. When these tables are used, with their explanatory notes as a base, it is necessary to add the diet which has been found suitable for the particular needs of each patient. His carbohydrate, protein, and fat tolerance should be stated definitely. The weight at which the diet is expected to maintain the patient should also be given. Arrangements must be made for urinalysis at certain intervals. Finally, the patient should be impressed with the fact that after a time it will be necessary to re-establish his tolerance and to adjust his diet to new conditions.

INSTRUCTIONS TO PATIENTS

The patient should bear in mind that diabetes is a disease in which the ability of the body to utilize carbohydrate material is decreased. Carbohydrates are largely contained in vegetables, cereals, meals, flours, and sugar, but they are also found in many animal foods. The food values given in the appended tables are not complete, but the list contains the practical foods of daily use. It is to the patient's best interest to secure all the knowledge possible of the preparation and percentage of food values.

In order that the greatest variety of food may be used with the least possible danger by the diabetic patient it is advised that he study the tables carefully and compute for himself proper substitutions with approximate accuracy. An accurate food scale should be procured and used until the ability is acquired to judge weights of given food by volume.

Vegetables should be cooked in two waters and weighed after cooking. In the main, it is to be remembered that the carbohydrate foods are the ones to be kept carefully to or below the amount prescribed. Proteins and fats are less harmful, but should not exceed the allotted amounts. Various foods enumerated in the table have high values in all three of the food constituents, namely, protein, fat, and carbohydrate; this must be taken into account in their substitution.

The urine should be examined as often as possible; this may be done by the patient himself, but preferably by the home physician. For the first month or two of treatment the examination should be made twice a week. The reappearance of sugar in the urine is an indication for a starvation day, followed by a return to the same diet with the carbohydrate allowance cut in half for one week. A steady decrease in weight from that estimated proper for the individual patient should be noted as an indication for an increase in the fat.

Hard work increases the demand for food consumption in the body, and is to be avoided, although the patient is advised to live as normally as possible under the circumstances. Many factors may occur to make it necessary to re-establish the tolerance; this should be done at the first sign of trouble which cannot be overcome by the adjustment of the diet by the patient himself. Even if no trouble is experienced, it is advisable for the patient to consult a physician competent to judge if the diet is still suitable for his needs. The ordinary breads have not been added to the diet, although reference to them is made in the tables. Their high content of starch makes them unsafe, and their use will necessitate the reduction of the total quantity of food allowed. All patent diabetic foods contain certain percentages of protein, carbohydrate, and fat, and none of them can be eaten in any quantity desired. There are many diabetic flours on the market, and before using one its percentage content should be carefully noted.

For all practical purposes 30 grams equal 1 ounce. The tolerance will be stated in grams, and the amounts of food allowed will be given in ounces. The 5 per cent. vegetables diminish in the cooking to about 3 per cent. of carbohydrate; this is taken into account in making up the diet. The carbohydrate allowance will be stated in amounts of 5 per cent. vegetables, but, except on the days which may be specifically stated, substitutions may be made of the 10 per cent., the 15 per cent., or the 20 per cent. groups by estimating the proper amounts to make equal values, that is:

1 ounce of 20 per cent. = 4 to 5 ounces of 5 per cent. vegetables.
1 ounce of 15 per cent. = 3 to 4 ounces of 5 per cent. vegetables.
1 ounce of 10 per cent. = 2 to 3 ounces of 5 per cent. vegetables.

Graham, rye, and white breads average about 50 per cent. carbohydrate.

CARBOHYDRATE VALUES

Vegetables and fruits, 5 per cent.	Asparagus	Lettuce
	Beet greens	Pumpkin
	Brussels sprouts	Radish
	Cabbage	Rhubarb
	Cauliflower	Ripe olives
	Celery	Sauerkraut
	Cucumbers	Sorrelo
	Eggplant	Spinach
	Endive	String beans
	Grape-fruit	Tomatoes
	Kohl-rabi	Unsweetened pickles
	Leeks	Water cress
Vegetables, fruits, and nuts, 10 per cent.	Beets	Onions
	Blackberries	Oranges
	Brazil nuts	Peaches
	Carrots	Pineapple
	Cranberries	Squash
	Lemons	Strawberries
	Mushroom	Turnip
	Muskmelon	Watermelon
	Okra	
Vegetables, fruits, and nuts, 15 per cent.	Apples	Green peas
	Apricots	Huckleberries
	Artichokes	Parsnips
	Beechnuts	Pears
	Canned lima beans	Pecans
	Cherries	Pistachios
	Currants	Raspberries
	Filberts	Walnuts
Vegetables, fruits, nuts, etc., 20 per cent.	Almonds	
	Bananas	
	Beans, baked	
	Beans, shelled	
	Corn, green	
	Macaroni, boiled	
	Plums	
	Potatoes	
	Rice, boiled	

SOURCES OF PROTEIN

Beef, mutton, pork, fish, fowl, cheese, eggs; for example:			
	Protein, per cent.	Fat, per cent.	
Beef and veal (boiled or roasted)	22.0	28.5	
Lean round steak	28.0	8.0	
Corned beef	15.5	26.0	
Sausage	19.5	18.5	
Mutton (or lamb)	25.0	22.5	
Pork:			
Ham (lean)	20.0	21.0	
Bacon	10.5	65.0	
Sausage	13.0	44.0	
Chops or roast	20.0	Varies according to amount of gross fat	
Fowl:			
Young chicken	21.5	2.5	
Old chicken	19.0	16.0	
Goose and duck	16.0	36.0	
Turkey	21.0	22.0	
Fish	15 to 19	2.0	
Gelatin	91.5	0	
	Protein, per cent.	Fat, per cent.	Carbohydrates, per cent.
Cheese:			
American, pale	29.0	36.0	
American, red	29.5	38.0	
Cottage	21.0	1.0	4.0
Full cream	26.0	34.0	2.5
Limburger	23.0	29.5	
Roquefort	22.5	29.5	2.0
Swiss	27.5	35.0	1.0

Eggs: One egg is equivalent to 1 ounce of lean meat in both protein and fat values.

SOURCES OF FAT

Butter, lard, rich cream, fat pork and bacon, oil, any fat meat; for example:		
	Fat, per cent.	Protein, per cent.
Butter and lard	85	
Rich cream	40	3.5
Fat pork and bacon	65	10.5

FLUIDS

	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.
Milk (skimmed)	3.5	...	5.0
Buttermilk	3.0	...	5.0
Milk (whole)	3.0	4.0	5.0

Bouillon or clear meat soups may be taken as desired.
Tea or coffee may be drunk clear or with the cream or milk allowance.

SYPHILIS OF THE STOMACH: REPORT OF A CASE

Symptomatology. Gastric Chemistry and the *x*-Ray. Diagnostic Criteria. Differential Diagnosis. Results of Treatment. Observations and Conclusions Based on a Study of 55 Cases

G. B. EUSTERMAN, M. D.

CASE I (A229712).—Mr. C. C. B., white, aged thirty-two, was admitted for examination May 1, 1918. This patient had been in good health until December, 1916, when he had "grip," and for several weeks afterward was bothered with more or less pain in the chest and right shoulder, and stiffness in the neck. He began to lose weight about this time and, although the pain disappeared, loss of weight continued. The latter was partly attributed to close work in a laundry. For the previous five months he had complained daily of a gnawing, dull, epigastric pain which appeared about two or three hours after meals and was relieved by eating. At times this pain radiated to the right subscapular region. Only once was the pain at night sufficient to awaken him. After several months the pain practically disappeared. For more than three months, however, before he was admitted to the clinic he vomited freely and no solids seemed to pass from his stomach. Nearly every morning before breakfast, particularly if solids had been eaten the day before, the patient experienced a full bloated feeling in the epigastrium, accompanied by belching and regurgitation of food, with no associated pain or nausea, but anorexia. This was soon followed by vomiting of nearly all the solid food eaten the day before, and some tasteless or slightly sour fluid, with relief from all distress and a desire to eat breakfast. If the patient partakes only of liquid food there is no vomiting or associated symptoms. Vomiting is often induced in order to relieve the epigastric discomfort.

The patient has not noticed blood in the vomitus or the feces. The local physician diagnosed healed ulcer in the pylorus, causing obstruction. During the last two months the bowel movements have been loose, about four movements daily, without pain, tenesmus, blood, or mucus. Further inquiry revealed no history of dysphagia, acute colicky pain, localized soreness, tetany, headaches, or urinary disturbances.

Family History.—A sister and a brother died at a very early age of pulmonary tuberculosis; the mother died of erysipelas at forty-eight; the maternal grandmother died of tuberculosis at fifty-three, one paternal uncle is insane, the father is living and well.

Personal History.—The patient, a male nurse, was married at the age of twenty-five and was divorced four years afterward; he has one healthy child; his former wife is also healthy. He uses coffee and tobacco to excess. He had tonsillitis as a child, malaria at the age of fourteen, gonorrhea at twenty-two, with urethral discharge for five months, but no complications, and "grip" in December, 1916; he denies syphilis.

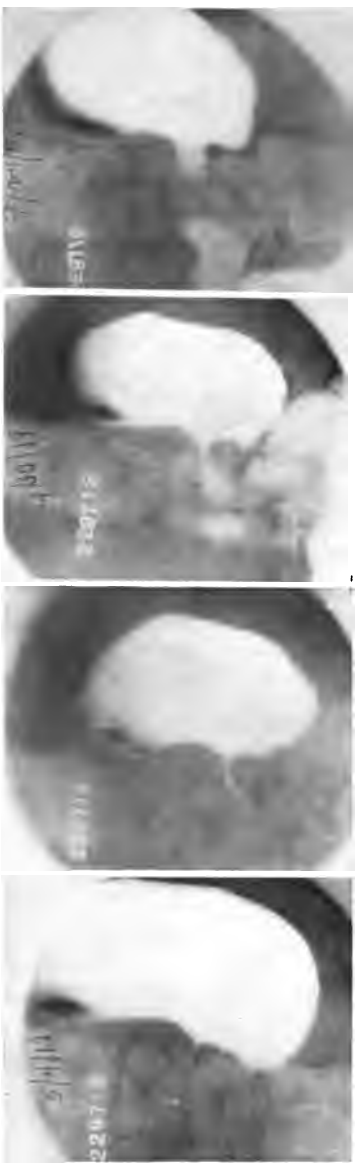
The physical examination, with one exception, which will be described later, was satisfactory. The patient was reduced from a normal weight of 165 pounds to a weight of 111 pounds, which represents a loss of weight over a period of one and a half years. The blood-pressure was subnormal; the pulse-rate normal, the heart action regular, and the temperature slightly subnormal. Several crowns and large fillings were found in the teeth. The tonsils revealed a low-grade inflammation with cheesy plugs in the crypts. The nervous, osseous, and cardiovascular systems were objectively negative. Adenopathy was not marked. The abdomen showed an absence of tenderness, resistance, and peristaltic unrest, but a succussion splash, and on deep inspiration a small, non-sensitive, movable ridge was palpable in the right epigastrium, quite distinct from the liver edge above it.

Urinalysis was normal, hemoglobin was 68 per cent., erythrocytes 4,880,000, and leukocytes 8400; the differential smear showed no abnormalitity.

Gastric analysis, May 4, 1918, twelve hours after a Riegel

motor test-meal and one hour before an Ewald test-meal, revealed a total acidity of 70, an absence of free hydrochloric acid, a filtrate measuring 600 c.c., poorly chymified, gross food particles, a slight trace of lactic acid, a few sarcinæ, but an absence of Oppler-Boas bacilli. Subsequently, after a thorough gastric lavage and gentle catharsis, the patient was put on a milk diet for three days, at the end of which time repeated guaiac and benzidin tests failed to reveal blood in the feces. From the fluoroscopic and *x*-ray examinations of the stomach, May 4, 1918, a diagnosis was made of operable cancer of the stomach, involving the pylorus; barium residue was marked after six hours (Fig. 134, *a*).

Apparently this was a case of an obstructing pyloric lesion in a comparatively young male adult. Because of the patient's age an obstructing benign chronic duodenal or gastric ulcer near the pylorus seemed most probable, but anachlorhydria and the filling defect in the pylorus, as revealed by the *x*-ray, argued almost decisively against such a condition. Benign obstructing ulcers in the third decade of life are invariably associated with marked hyperacidity and hypersecretion, or at least normal acidity. In elderly patients with ulcer, advanced associated gall-bladder or pancreatic disease may depress gastric chemism sufficiently to produce anacidity. Linitis plastica (fibromatosis, gastritis granulomatosa fibroplastica) was possible but not probable, owing to the rapidity of the clinical course and the early obstruction. Tuberculosis of the stomach is so extremely rare that it was not considered in the diagnosis. Thus far only 2 cases have been found in 6500 operations on the stomach performed at the clinic; both of these were associated with pulmonary tuberculosis. Syphilis of the stomach had not as yet been excluded. I have previously shown that a palpable tumor is unusual in such cases.[2],[3] In about 50 to 60 per cent. of all proved gastric carcinomas a tumor is palpable, in contrast to 15 per cent. in the syphilitic cases. Food or barium residue of variable degree is present in an average of 60 per cent. of gastric cancers, in about 30 per cent. of gastric ulcers, and in 23 per cent. of the syphilitic cases. The gastric chemistry of



a b c d

Fig. 134.—Case 229712. *a*, May 4, 1918. Filling defect in the pylorus, with a corresponding palpable "ridge" characteristic of cancer. Small six-hour barium residue. *b*, May 29, 1918. Condition unchanged. *c*, April 30, 1919. Condition unchanged, but no residue and disappearance of palpable ridge. *d*, September 24, 1919. Condition greatly improved. No residue and no palpable ridge.

proved gastric carcinomas in all stages shows free hydrochloric acid in 48 per cent., although usually subnormal, but free hydro-

chloric acid is absent in 80 per cent. of all gastric syphilitic cases. In this case, therefore, benign gastric ulcer was excluded on the basis of the patient's age, and especially on account of the *x*-ray findings and gastric chemistry. Linitus plastica was not excluded, but was highly improbable. Gastric carcinoma seemed the most possible diagnosis except that the patient was rather young, and although he was moderately anemic and undernourished he was not cachectic. While the absence of free hydrochloric acid with the associated pyloric obstruction and tumor favor carcinoma, gastric syphilis seemed possible in view of the patient's age and general appearance.

Various factors must be considered in determining the specific nature of a gastric lesion. The criteria of diagnosis are as follows: (1) Positive Wassermann reactions; (2) evidence of syphilis elsewhere in the body; (3) demonstration of a lesion in the stomach by the *x*-ray, and (4) improvement following therapeusis.

On May 8, 1918, and at a second examination the following day the Wassermann reaction was strongly positive. The patient then admitted that he had had a small, genital sore seven years previously, without definite skin or mucous membrane secondaries, and that he had noticed some crusting of the skin about the right elbow the year following. Under the olecranon process of the right elbow a somewhat white atrophic scar not distinctive of a luetic process was found. Several scars on the penis and one on the dorsum, however, are characteristic. The scrotum also showed much scarring and a white patch, suggestive of an arciform outline. The general impression was that of an old nodulo-ulcerative process.

On May 25th the patient had received three intravenous treatments of arsphenamin, 0.3, 0.4, and 0.5 gm. respectively. The patient said that following the last treatment the subjective sensation of obstruction had been relieved and that he was able to partake of solid food without vomiting or distress and had gained 10 pounds. A reray showed only a slight six-hour barium retention (Fig. 134, *b*); a gastric analysis ten hours after a motor meal showed: total acids, 20; no free hydrochloric acid; no

food residue. The palpable ridge persisted indistinctly and corresponded to the filling defect in the pylorus.

This patient came under my observation again April 28, 1919. Up to and during this time he had received ten intravenous treatments of arsphenamin in addition to 100 mercurial inunctions, without renal or cutaneous complications. The Wassermann test again showed a positive reaction, and further treatment was arranged. The patient had gained 47 pounds in weight and had no qualitative or quantitative distress. Physical examination, exclusive of the healed cutaneous lesions, was practically negative and the "ridge feel" in the epigastrium had

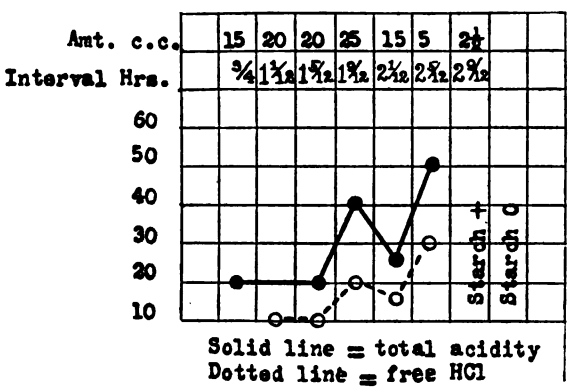


Fig. 135.—Fractional gastric analysis.

disappeared. The bowels acted normally. The patient slept well, had a good appetite, and was not nervous. There were no urinary disturbances.

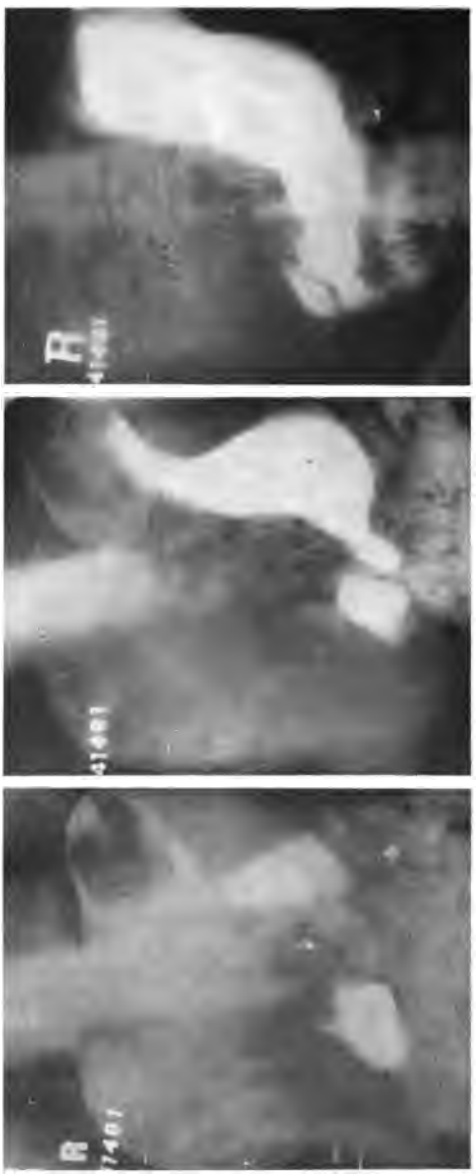
Gastric analysis at this time showed a return of acids and ferments. The total acidity at the end of an Ewald test-meal was 20, the free hydrochloric acid was 14. A second titration revealed a total acidity of 28, free hydrochloric acid 20, and a total filtrate of 80 c.c. The *x*-ray showed the general condition unchanged, but without retention (Fig. 134, *c*). Up to September 24th the patient had received 15 intravenous arsphenamine treatments and 144 mercurial inunctions under the direction of the Department of Dermatology and Syphilology. Several

months after treatment the Wassermann reaction was again positive, necessitating further treatment. Our experience with other patients having active visceral lesions have been similar. Careful serologic supervision and antispecific treatment intermittently over a period of three years, at least, is necessary.

The function of this patient's stomach continued perfect. His infected tonsils and four devitalized teeth with periapical infection had been removed without incident. The *x*-ray findings of September 24, 1919, as shown in Fig. 134, *d*, revealed definite anatomic improvement and good motility. The gastric analysis, the same day, determined by a fractional analysis, is illustrated in Fig. 135. There has been a reappearance of the free hydrochloric acid. The complete emptying time of the stomach following a modified Ewald meal was about two hours and twenty minutes.

DISCUSSION

This case is interesting for several reasons. In the first place, the patient is again in gastric health following purely antispecific treatment. The anatomic restitution has not been complete, but this is explained by the fact that organized sclerotic tissue had supplanted granulomatous or inflammatory tissue, an attempt on nature's part to heal the lesion before the patient came under our observation. Such patients when seen in a purely exudative stage may not only be clinically but also structurally cured, as pictorially shown in Fig. 136, *a*, *b*, *c*. In a number of cases under the influence of specific treatment the clinical improvement has been entirely out of proportion to the organic changes. Such clinical improvement is prompt and definite after the first few intravenous injections. No adequate explanation has been offered thus far for this phenomenon. The specificity of this lesion seems to have been proved, as all the requirements previously mentioned have been fulfilled; there is a history of definite infection, consistent Wassermann reaction, clinical and roentgenologic evidence of gastric disease, the presence of a demonstrable cutaneous healed lesion characteristic of



a b c

Fig. 136.—Case 41491. *a*, October 11, 1915. Condition of the stomach at the time of examination. *b*, Examination after six weeks' antiluetic treatment; marked improvement. *c*, Examination at the end of a year revealed a normal stomach.

syphilis, and therapeutic as well as structural improvement of a permanent nature.

The return of hydrochloric acid and gastric enzyme is of further interest. It has been almost consistently observed that once the acid and enzyme have disappeared, from whatever cause, they rarely return. Free hydrochloric acid was absent in 80 per cent. of our cases of gastric syphilis; and in the remaining 20 per cent. free hydrochloric acid was present usually in subnormal titrable strength; in 7.5 per cent. of this latter group achylia alternated with free hydrochloric secretion.

The presence of a palpable gastric tumor, anacidity, and pyloric obstruction invariably spells gastric carcinoma, especially when associated with a definite filling defect on the *x*-ray plate. In our experience the other most probable lesion was gastric syphilis; but the incidence of tumor and obstruction is uncommon in this lesion, less frequent than in benign obstructing ulcers, and three times as rare as in malignant gastric disease. While the pyloric third of the stomach seems to be the usual site of involvement in acquired gastric syphilis, the rarity of a palpable tumor and obstruction is perhaps best explained by the fact that circumscribed gummatous granuloma is a relatively unusual formation. From a study of the roentgenograms and the results of therapy in cases in the earlier stages of this disease we have gained the impression that visceral syphilis is a patchy or diffuse progressive, irritative, or inflammatory process. This view is strengthened by Warthin's exhaustive and convincing studies. Unfortunately, there is no opportunity for more intensive tissue study of this disease, as it affects the stomach in all its stages. The microscopic examination of the resected portions of the stomach in advanced cases, as I reported briefly in my first contribution, showed chiefly a marked fibrosis of the thickened muscularis and hypertrophied submucosa with atrophy of the mucous membrane. Characteristic perivascular lymphocytic infiltration with consequent obliteration of the smaller blood-vessels and frequent sclerosis of the larger vessels was also noted. (This resulting vascular change probably explains the rarity of gróss hemorrhage, as it occurs approximately in only 5 per cent.) In the advanced cases the stomach was found, grossly, to be a thickened, shrunken,

and deformed organ, often with a tendency to hour-glass contraction.

In numerous instances the syphilitic lesion seemed fairly confined to the pylorus or it extended along the lesser curvature to and including the pars media. In one case it was confined chiefly to the upper third, along the lesser curvature. In the congenital cases the roentgenograms plainly revealed a uniformly and completely involved organ, no doubt a diffuse interstitial process which resulted in a short stiffened tube having the circumference of a small child's wrist. On several occasions multiple ulcers in the stomach together with a patchy regional infiltration of the gastric wall as seen at the operating-table give rise to the suspicion of a syphilitic etiology subsequently confirmed by clinical, serologic, and therapeutic investigation. Such cases would have made interesting material for a histopathologic study, but resection would have been inappropriate. These are invariably cases in an early stage of the disease; they are of clinical interest because the chemical and *x*-ray characteristics and the nature of the complaint are more like those of ulcus carcinomatosum or early scirrhous cancer. The niche, or accessory pocket and incisura of the benign calloused ulcer, are uniformly absent in our experience, probably due to the shallow depth of the specific lesion and the regional diffuse infiltration of the submucosa. Benign calloused ulcers are rarely multiple in the same organ; concurrent benign gastric and duodenal ulcers occur in about 3 per cent. of all cases. The prognosis as to clinical cure or improvement in so far as the stomach is concerned in cases showing extensive diffuse involvement of the organ, often with a markedly reduced capacity, in my opinion, depends chiefly on the duration of the gastric symptoms. Figure 136, *a* shows the involvement to be extensive to a discouraging degree. The gastric capacity was reduced to a maximum of 6 ounces; the period of gastric complaint, however, was not more than eight months, although the disease had been acquired eight years previously, and had been treated very inadequately during that time. Under intensive treatment in our hands a symptomatic cure was quickly established, and anatomic restoration

was completed within twelve months. Unfortunately, such brilliant results are seldom obtained, as the diagnosis is not made early enough. Notwithstanding this, cure and improvement have been recorded in 70 per cent. of a series of 55 patients treated medically or operated on, or both. There is little hope for structural improvement in cases of heredosyphilis unless the patients are treated before the second decade of life.

From the standpoint of symptomatology there are no distinguishing features, the symptoms depending logically on the site and extent of the involvement. In this particular case the symptoms, as would be expected, were those of benign or early malignant, pyloric obstruction. In the involved or advanced non-obstructed cases the patients have symptoms approaching the characteristics of a slowly progressive form of scirrhous carcinoma. Patients with high obstructing hour-glass stomachs usually have considerable pain and vomiting after taking food. The common symptoms in all of these cases are: a fairly marked progressive course, pain soon after eating, invariably associated with nausea and vomiting, the absence of gross hemorrhage, maintenance of appetite in the majority of cases, and marked loss of weight without definite cachexia. The average age of these patients is thirty-five years. The average duration of their gastric disturbances is about two years, in contrast to the average age of the ulcer-bearing patient, which is about forty-five and the average duration of symptoms ten and a half years, and the cancer patient, whose average age is fifty-four and the average duration of symptoms is one and a half years.

The conclusions drawn from proved cases of acquired gastric syphilis are that the patient is in the third decade, with marked and progressive disturbances of comparatively short duration, a gastric chemism of advanced carcinoma and roentgenologic characteristics, as described by Carman, usually revealing marked organic changes. Invariably, however, cachexia, a palpable mass, and anorexia are absent, whereas they are usually present in gastric carcinoma with the same degree of involvement. The diagnosis is often made by inference or by bearing the possibility of gastric syphilis in mind.

BIBLIOGRAPHY

1. Carman, R. D.: Syphilis of the Stomach in its Roentgenologic Aspects, Amer. Jour. Syph., i, 111–116, January, 1917.
2. Eusterman, G. B.: Syphilis of the Stomach: a Report of 40 Cases in which there were Demonstrable Lesions and Therapeutic Cure or Improvement, Amer. Jour. Syph., ii, 205–219, April, 1918.
3. Eusterman, G. B.: Syphilis of the Stomach: a Clinical and Roentgenological Study with a Report of 23 Cases, Amer. Jour. Med. Sci., cliii, 21–39, January, 1917.
4. Warthin, A. S.: The New Pathology of Syphilis, Amer. Jour. Syph., ii, 425–452, July, 1918.

PANCREATIC CARCINOMA

R. D. MUSSEY, M. D.

CARCINOMA of the pancreas is a disease of relative infrequency. Cantlie reported 15 cases of primary carcinoma of the pancreas in 4100 necropsies made at Charing Cross Hospital in London, and Segré, 127 cases of pancreatic carcinoma in 11,472 necropsies. Osler and McCrae state that carcinoma of the pancreas occurs once in 60 cases of malignancy in males, and once in 100 cases in females. This incidence must put the diagnostician on his guard, the more so on account of the insidious onset of the disease. While some cases present the typical syndrome of Chauffard, many others lack some of these symptoms, and are extremely difficult of diagnosis.

The typical syndrome, as outlined first by Chauffard, in 1908, and next in this country by Ferguson, in 1910, is briefly as follows: Digestive disturbances, deepening jaundice, loss of strength and weight, the presence of a distinctly distended gall-bladder, and pain, in persons of middle age. Chauffard, especially, emphasizes the element of pain, which occurs particularly when the carcinoma is in the body of the pancreas; it is the most significant symptom, having characteristic features which the pain of other upper abdominal lesions usually does not possess. Leriche, quoting Chauffard, describes the pain as starting under the left costal margin, working toward the epigastrium, deeply situated, sometimes more severe in paroxysms, having a "corset constriction" sensation, most nearly resembling tabetic crises.

A review has been made of the cases of pancreatic tumor, in which operation was done in the Mayo Clinic up to January, 1919; these cases were diagnosed grossly as carcinoma at the time of operation. The purpose of this review is to establish, if possible, the characteristics of the element of pain in pan-

creatic carcinoma. Other symptoms of the disease were noted at the same time. In order, if possible, to have uncomplicated symptoms, the 90 cases chosen are those in which the tumor was found to have originated in the pancreas, and in which involvement of the stomach or gall-bladder did not obscure the diagnosis.

While practically all patients exhibited malaise, lack of appetite, loss of weight and energy common to carcinoma of the digestive tract, pain was the outstanding feature.[8] It was the chief complaint in 44 per cent. of the cases. The symptoms next in frequency were gastric disorders 24 per cent., and jaundice 21 per cent. Pain occurred in 88 per cent., or in all but 10 cases. This pain was usually described as deep, dull, boring, of moderate severity, peculiarly nagging, apparently without cause, generally very difficult to relieve, and occurring most often in the left upper abdomen. In 32 per cent. of the cases it also radiated to the back, a lower incidence than that associated with cases of gall-stones, in which pain radiating to the back is found in 55 per cent. Constancy of pain, an important characteristic of pancreatic carcinoma, was noted in 47 per cent. of the cases; in some of these the pain was worse in spells. In the remaining 53 per cent. the pain occurred in spells alone. The constancy and intractibility may be due to pressure on or involvement of the solar plexus.[9] There was little relationship between pain and the ingestion of food in our cases, as in relatively few the pain was increased and still more rarely eased by food.

"Stomach trouble" was the chief complaint in 24 per cent. of the cases. The loss of appetite, distress after eating, bloating, with eructations of gas, and more rarely vomiting, are symptoms similar to those in gastric malignancy.

Jaundice occurred in 41 per cent. and was constant in all but 5 cases. This incidence varies from Opie's report of 82 cases with jaundice of 113 cases of carcinoma of the pancreas. Jaundice was rarely coincident with the onset of pain; most often it had no relation to it, although it occurred in but 6 of the patients who had no pain.

The physical examination shows in the typical case a patient

(80 per cent. of ours were males) past middle age, the average being fifty-six years, with evidence of cachexia and pallor or jaundice. He is weak, has lost weight, averaging 26 pounds in an illness of only a few months' duration. No other physical findings are noteworthy except the abdominal examination. This may reveal an epigastric mass, elongated, and usually not moving with respiration. A mass was found in 56 per cent., associated with abdominal resistance and tenderness in 30 per cent. of the cases. In many of the jaundiced patients an enlarged liver and a distended gall-bladder were demonstrated. In 31 of the 37 patients with jaundice, in agreement with Courvoisier's law, some enlargement or distention of the gall-bladder was found at operation.

In many respects the clinical history of pancreatic carcinoma is similar to that of gastric carcinoma unless a history of jaundice is obtained. The test-meal and the Roentgen ray are of especial value in differentiating the two conditions, and the palpation of the immovable mass may aid in making the diagnosis. A test-meal was taken in 54 of the 90 cases. Free hydrochloric acid was found in 35 of these, 65 per cent., as compared to cases of gastric carcinoma in which free hydrochloric acid was found in only 46 per cent.

Case histories have been selected to illustrate the various types of the disease.

CASES

CASE I (169687).—A man aged fifty-seven came for examination complaining of jaundice and lassitude. Previous illnesses were unimportant. For five or six months he had had more or less constant pain below the ensiform, extending through to the back on the left side and radiating around the left ribs to the back, with some tenderness below the right rib margin. The pain was not severe, but was aggravated by jolting. He had a bad taste in the mouth and had had no appetite for two months. There had been no sour eructations or vomiting. The jaundice had come on gradually six weeks before and had continued to be quite uniform. He had itching of the skin. The stools were clay colored. There had been no attacks of colic.

The patient complained of a heavy dull feeling and of having lost considerable weight, but he was fairly well, and without heart, lung, or urinary trouble.

Physical examination showed a man in a fair general condition, weighing 130 pounds, with a loss of 20 pounds in five months. The jaundice was marked and the skin showed itch-marks. The liver was normal in size and the gall-bladder large, tense, and palpable. The remainder of the findings, aside from that of bile in the urine, were negative.

Operation revealed a carcinoma of the pancreas with obstruction of the common duct in the head of the pancreas. The gall-bladder was very large, being distended with bile. A cholecystogastrostomy was performed.

CASE II (159596).—A man aged fifty-seven consulted us on account of a stomach complaint. He had had scarlet fever as a child and an occasional attack of what may have been the grippe. Five weeks before examination he began to notice a griping pain in the abdomen associated with some pain in the epigastrium. The pain was not lessened at night until 12 or 1 o'clock, and he could not find a comfortable position. Food lessened the pain somewhat, and he believed that he would be relieved if he could empty his stomach. He avoided heavy and fried foods and fruits. He had a good appetite and no sour eructations. The trouble had been present almost constantly since its onset. Twenty-five years before he had had a somewhat similar attack of indigestion which had improved with care and diet.

Examination revealed a well-nourished man weighing 153 pounds, who had lost 10 pounds in five weeks. He was slightly pale. There was some fulness and resistance in the right epigastric area. Palpation discovered a somewhat transversely elongated mass not moving with inspiration. The test-meal showed no free hydrochloric acid. *x*-Rays of the stomach, kidneys, and colon failed to reveal any abnormal condition.

On exploration, a carcinoma of the body of the pancreas with a secondary nodule in the gastrohepatic omentum was found.

CASE III (172143).—A man aged sixty-two came to the clinic complaining of jaundice with recent pain. He showed a distinct loss in weight and strength; he had been in vigorous health up until shortly before and his appetite had remained good until three months before. Since then he had had a dull pain in the epigastrium with an uncomfortable sensation of bloating coming on directly after meals and lasting two or three hours. During the last twelve days the pain had come sooner after meals and was more severe. It was associated at times with vomiting, and two weeks before examination he had vomited a coffee-colored fluid. He had been jaundiced for ten days; since then the stools had been clay colored. A mass had been present in the right upper abdominal quadrant for two to three months.

Examination showed a moderatley emaciated man weighing 146 pounds; he had lost 34 pounds in weight in six months. Jaundice was marked and definite scratch-marks were found on the skin. There was an enlargement in the region of the liver and below this a mass which seemed to be a palpable gall-bladder.

Exploration revealed a tumor at the head of the pancreas producing a complete obstruction of the common duct. The gall-bladder was greatly distended. A cholecystogastrostomy was performed.

CASE IV (169066).—A woman aged forty-eight consulted us because of loss of appetite and general energy. She had had typhoid fever twenty years before and shortly afterward an illness diagnosed malaria. She had been married thirty years and had had six children. Her general health had been good until four months prior to the examination, at which time she began to lose her appetite and to have discomfort and a constant heaviness in the epigastrium, which did not amount to pain. She had not noticed whether or not food increased the discomfort, although occasionally during the past two months she had vomited after eating. She had been living on milk and soups, as she could not take solid foods. The jaundice, which also had begun four months before, had grown progressively deeper with

the loss of weight and strength. The urine was highly colored and the stools lightly colored. There had been no itching of the skin.

Examination revealed a poorly nourished woman, weighing 122 pounds, having lost 32 pounds in weight in three and a half months. She was moderately jaundiced. The liver was palpable at least two fingerbreadths below the costal margin, and a dense cystic mass was palpable in the gall-bladder area. Bile was found in the urine. The hemoglobin was 52 per cent. A test-meal showed the total acids to be 30, free hydrochloric 16. An *x*-ray examination of the stomach did not reveal any pathologic condition.

Abdominal exploration revealed a tumor at the head of the pancreas of undoubted carcinomatous nature. The common duct and cystic duct were markedly dilated and the gall-bladder was very much distended. A cholecystogastrostomy was performed.

CASE V (239186).—A man aged sixty-one complained of pain in the right abdomen associated with jaundice. He had had no previous illness aside from typhoid fever at the age of ten. Five months prior to examination he had a sudden severe attack of pain in the right epigastrium which was called acute indigestion, associated with marked constipation and lasting about two weeks. The diarrhea which began at that time had continued. About six weeks after its onset the patient became jaundiced, and this condition persisted. Three weeks before examination he began to have pain in the right hypochondrium. His appetite was very poor, he vomited some bile, had considerable belching, and some hiccup. The stools were light colored.

Examination revealed a deeply jaundiced and undernourished man. The liver and gall-bladder were both palpable. Examination of the urine showed bile. The *x*-ray examinations of the stomach and gall-bladder were reported as negative.

Abdominal exploration revealed a carcinoma at the head of the pancreas with biliary cirrhosis. The gall-bladder was distended with bile. A cholecystogastrostomy was performed.

DISCUSSION

Given a patient with a typical history of pain, deepening jaundice, immovable epigastric mass, an enlarged liver, and a distended palpable gall-bladder, and the diagnosis of pancreatic carcinoma may be made with reasonable certainty. Many of these patients, presenting themselves at the clinic, did not come to operation. It may be possible that the duodenal methods of differential diagnosis of biliary and pancreatic disease, as outlined by Einhorn and Crohn, could have eliminated a few more. For many of the patients with jaundice (23 of 40 have been operated on in the last three years), however, the operation was done as a palliative measure in an attempt to join the gall-bladder to the stomach or bowel in order to relieve the intense jaundice and its attendant suffering.

In the cases without jaundice or interference with pancreatic function the diagnosis is most difficult. In these cases particularly a careful symptomatic history may be of most value in the diagnosis. The Cammidge reaction and various tests of the pancreatic function have not been found to be of any great value.[11]

CONCLUSIONS

1. The most noteworthy characteristic of carcinoma of the pancreas is the constancy and steadily increasing severity of the symptoms.

2. Pain is of a more constant deeper type, and less influenced by food or measures of relief than in any other abdominal lesion.

3. Jaundice, while rarely occurring without pain, is not often related to its time of onset.

4. In the course of the routine examination of the 90 cases of this series, sugar was found in the urine in only 4.

BIBLIOGRAPHY

1. Cantlie: Quoted by Ferguson, A. H.
2. Chauffard, A.: Le cancer du corps du pancréas, Bull. de l'Acad. de méd., lx, 3 s., 242–255, 1908.

3. Crohn, B. B.: New Growths Involving the Terminal Bile and Pancreatic Ducts. Their Early Recognition by Means of Duodenal Content Analyses, Amer. Jour. Med. Sci., cxlviii, 839–856, December, 1914. The Early Diagnosis of Carcinoma of the Bile and Pancreatic Ducts, Amer. Jour. Surg., xxix, 270–274, July, 1915.
4. Einhorn, M.: Direct Examination of the Duodenal Contents (also Bile) as an Aid in the Diagnosis of Gall-bladder and Pancreatic Affections, Amer. Jour. Med. Sci., cxlviii, 490–495, October, 1914.
5. Ferguson, A. H.: Carcinoma of the Pancreas, Surg., Gynec., and Obst., x, 393–396, April, 1910.
6. Leriche, R.: Etude clinique sur le cancer du corps du pancréas, Lyon chir., iv, 261–279, September, 1910.
7. Opie, E. L.: Carcinoma of the Pancreas, Diseases of the Pancreas, Philadelphia, Lippincott, 288–298, 1910.
8. Osler, W., and McCrae, T.: Carcinoma of the Pancreas, Modern Medicine, Philadelphia, Lea and Febiger, iii, 648–654, 1914.
9. Packard, M.: Symptoms and Diagnosis of the Body and Tail of the Pancreas Suggestive Sign, with Report of a Case, New York Med. Jour., xcv, 742–744, April 13, 1912.
10. Segré, R.: Studio clinico sui tumori del pancreas, Ann. univ. di med. e. chir., cclxxxiii, 3–62, 1888.
11. Willis, B. C., McGrath, B. F. (et al): Clinical Experiences with the Cammidge Reaction, Surg., Gynec., and Obst., xi, 156–159, August, 1910.

RETROPERITONEAL TUMORS: REPORT OF TWO FIBROMYOMAS

J. A. H. MAGOUN, JR., M. D.

BECAUSE of the suspected rarity of retroperitoneal fibromyomas a stimulus was given to investigate the literature with reference to these tumors in particular, to retroperitoneal tumors in general, and to report the 2 cases recently observed at the Mayo Clinic. Singularly enough, these are the only cases of retroperitoneal fibromyomas that have been noted in the clinic in many thousands of routine examinations of the abdomen and pelvis. The clinical history of these two patients is as follows:

CASE 281037.—M. L., a man aged thirty-four (farmer), was examined at the clinic July 28, 1919. The patient had fallen from a horse nine years before, but gave no definite data regarding the injury. He complained chiefly of pain in the back and in the right iliac fossa, which had lasted three years. The pain was constant, but made worse by lifting. Pressure in the region of the right iliac fossa produced the sensation of needle pricks through the anterior part of the right leg. A swelling in the right iliac fossa had existed two years. The patient was constipated; his appetite was poor, and he had lost about 20 pounds in weight since the beginning of his symptoms. The systolic blood-pressure was 130; the diastolic was 70; pulse 80, and temperature 99° F. The teeth were in poor condition; the tonsils were red. The right epitrochlear gland and the right and the left inguinal glands were palpable. A mass about 14 by 10 cm. was discovered firmly fixed in the lower right abdomen, probably retroperitoneal. Other findings and symptoms were unimportant.

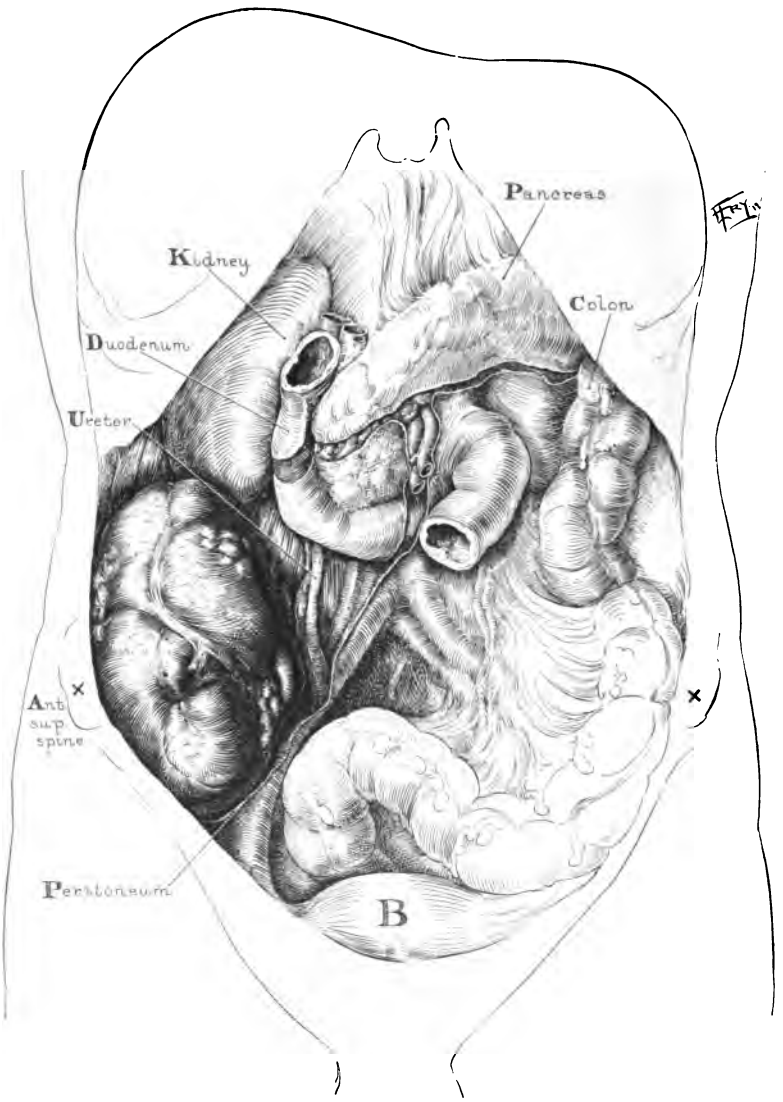


Fig. 137.—Case 281037. Fibromyoma as found at operation.

A clinical diagnosis was made of a right-sided abdominal mass. While the length of time since the growth had been noticed contraindicated sarcoma, it was, nevertheless, believed to

Fig. 138.—Case 281037. Encapsulated tumor 14¾ by 8¾ by 7½ cm., grayish white with areas of pink scattered throughout, firm, small, and non-nodular.

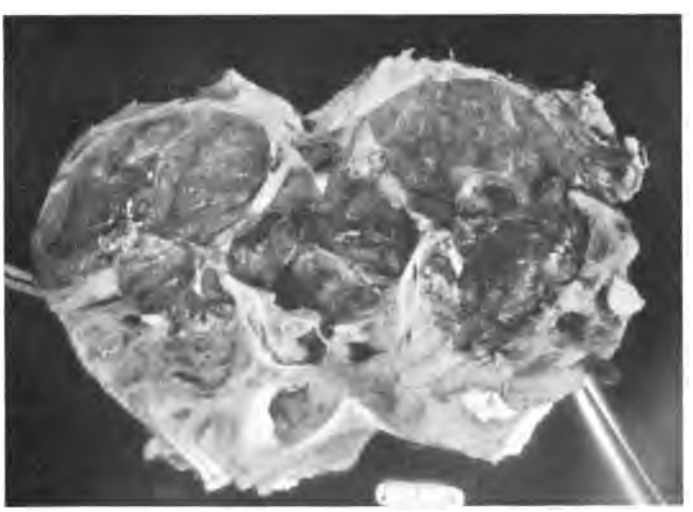


Fig. 139.—Case 281037. Cut section of specimen showing hemorrhagic cystic degeneration with serous fluid contents, also areas of yellowish-white fibromyomatous tissue.

Fig. 140.—Case 281037. Photomicrograph. × 50.

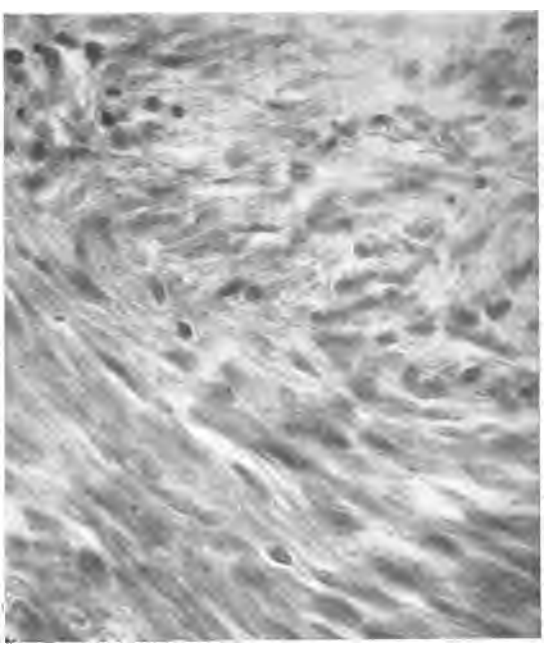


Fig. 141.—Case 281037. Photomicrograph. × 500.

be a retroperitoneal sarcoma. The patient had the fever characteristic of sarcoma, and complications of the kidney and colon had been ruled out by the negative cystoscopic and *x*-ray findings.

At operation a retroperitoneal tumor about 8 inches in diameter was found in the region of the right flank just at the outer side of the cecum (Fig. 137). The growth was hard and firmly attached posteriorly to the spinal muscles. The pathologist reported hemorrhagic, edematous, degenerating myoma (Figs. 138–141).

The patient's convalescence was uneventful, and he left the clinic fifteen days after operation.

CASE 274449.—W. J., a man aged thirty-seven (miner), was examined June 11, 1919. This patient's back had been injured twelve years before. About six years later he began to complain of moderately severe, fairly constant pain across the lower back and radiating down the left thigh. This seemed to be getting worse and he had been unable to work for several months because of pain and weakness in the back and thigh. Two months before he came to the clinic his bladder had been explored for tumor through a suprapubic incision. The surgeon who performed the operation thought he had sarcoma of the prostate and closed the wound without surgical interference. He had no pain in the perineum or urinary symptoms; his bowels were regular. He had lost 15 pounds in weight within the past year. He appeared anemic, but well nourished. His teeth were in poor condition. The systolic blood-pressure was 140, the diastolic 80. Urinalysis, blood count, cystoscopic, and *x*-ray findings were practically negative.

Rectal examination revealed a mass the size of a fist beneath the mucosa just above the prostate and seemingly involving the prostate. The tumor was hard, smooth, and firmly attached, probably to the right sacral wall. A clinical diagnosis was made of probable inoperable sarcoma.

At operation June 20, 1919, it was impossible to expose the tumor satisfactorily through a perineal incision. The urethra

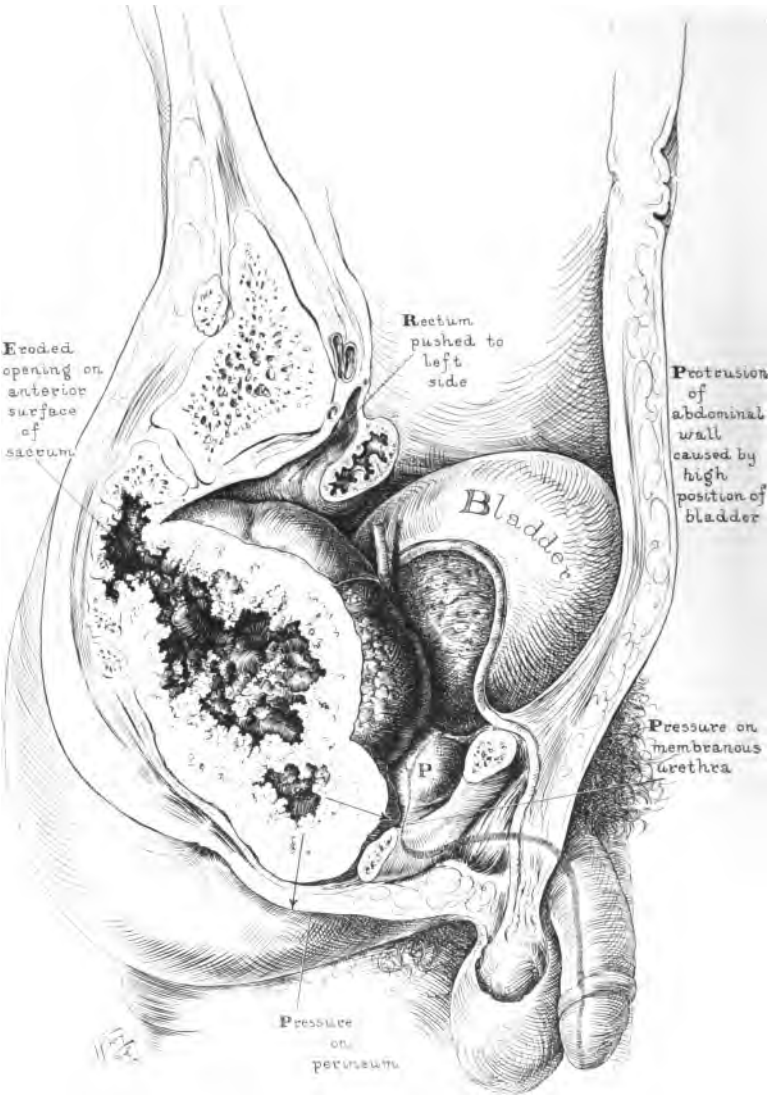

Eroded opening on anterior surface of sacrum
Rectum pushed to left side
Protrusion of abdominal wall caused by high position of bladder
Bladder
Pressure on membranous urethra
P
Pressure on perineum

Fig. 142.—Case 274449. Fibromyoma as found at operation.

was opened and found to be considerably deformed, the tumor having almost closed it. The growth was hard and rounded and it seemed as though it might be removed; it did not appear

to be malignant. It seemed best to allow this wound to heal and then to do an abdominal exploration.

A month later a solid tumor about 11 by 10 cm. was exposed, lying in the pelvis, in front of the sacrum (Fig. 142). The tumor had caused erosion to such an extent that two fingers could be passed into what apparently was an eroded opening into the anterior part of the sacrum. The growth was adherent and

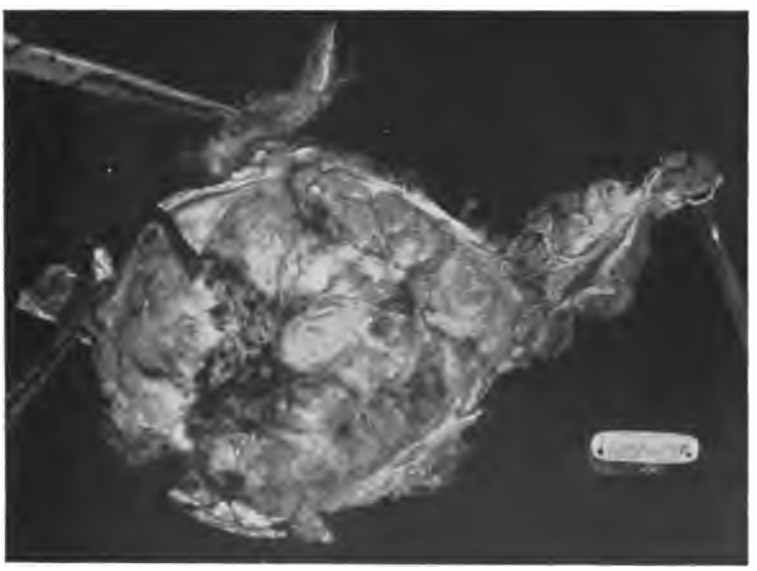


Fig. 143.—Case 274449. Tumor 11¼ by 10 by 3¾ cm., grayish white in appearance, firm, and smooth. Cut section shows smooth, yellowish-white fibromyomatous tissue. The tumor was not definitely encapsulated.

firmly encapsulated; it had to be broken and removed in pieces. The urethra was so completely obstructed that it was necessary to do a suprapubic cystostomy. It was impossible to tell just where the tumor had originated. The pathologist reported the growth to be a fairly cellular myoma (Figs. 143–145).

A review of the indexed English, French, German, and Italian literature on retroperitoneal tumors seems further to corroborate the rarity of true retroperitoneal myomas. Lockwood defines

the condition as "a solid or cystic tumor growing behind the peritoneum, into its fold and not connected with any of the great retroperitoneal organs." Five cases only were found reported in the literature.

Ogston, in 1896, reported a case in which the left ureter was involved; the sex of the patient was not stated.

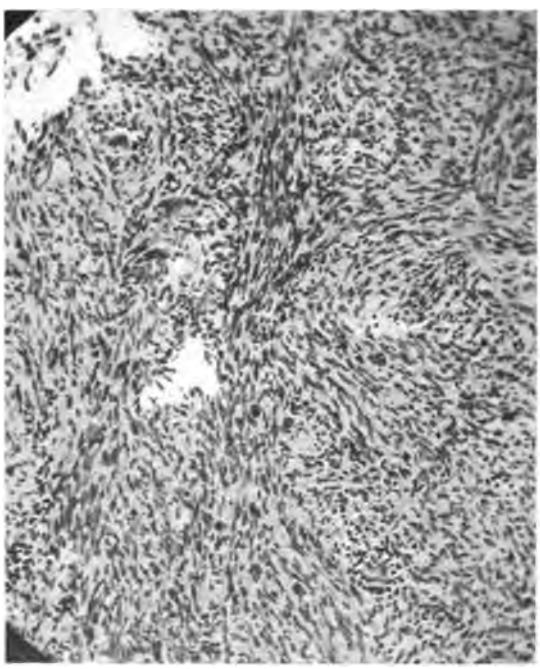


Fig. 144.—Case 274449. Photomicrograph. × 100.

Pfannenstiel, in 1897, reported the case of a woman with two retroperitoneal tumors; both were edematous hemorrhagic myomas, which he believed had arisen from the descending portion of the large bowel. The uterus was not diseased.

Fiori, in 1904, reported the case of a woman aged fifty-three who had a large fibromyoma of the uterus and a large retroperitoneal myoma which was in no way connected with the uterine tumor. Fiori, in discussing the possibility of metastasis,

says: "It would seem very strange, to say the least, if the tumor had been able to furnish transplants in the retroperitoneal tissues and not have involved any other visceral localizations, the kidney, lungs, and liver, which are usually considered as the seat of choice for metastasis of malignant neoplasms of the uterus."

Uchida, in 1912, recorded cases of Döderlein's and Van Latte's, a retroperitoneal myoma in a woman, and an adeno-

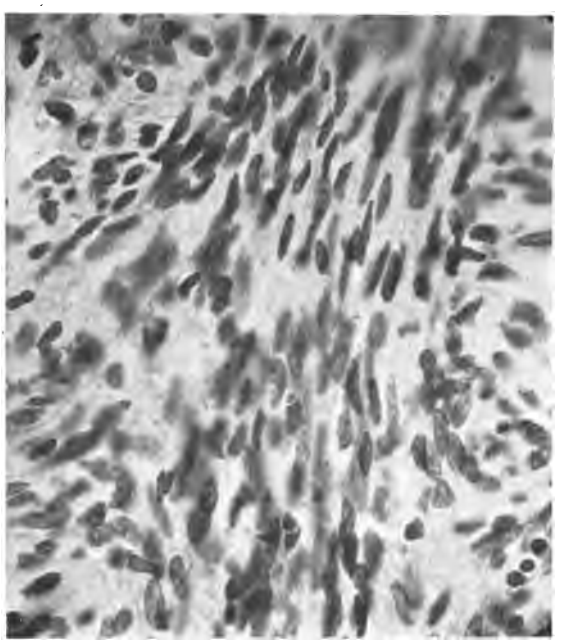


Fig. 145.—Case 274449. Photomicrograph. × 500.

myoma with sarcomatous degeneration in a patient whose sex was not stated.

Schlangenhaufer, in 1902, reported a fibromyoma of the uterus with metastasis of true myoma in the liver and lungs. He mentions five earlier authors as having each reported a metastasized true myoma. The cases are as follows:

1. Orth: Fibromyoma of the uterus with multiple metastasis.

2. Klebs: Fibromyoma of the uterus with metastatic tumor.

There was some question in this case as to whether the metastatic tumors were true myomas, for they contained endothelial cells. Klebs considered them of a myoblastic nature.

3. Langerhans: Fibromyomas of the uterus with metastasis in the lung.

4. Hansemann: Myoma of the stomach with metastasis in the liver.

5. Winkowski: Fibromyoma of the uterus; metastasis in the liver and the lung two years after the removal of the primary growth.

It seems to be the consensus of opinion that true myomas do not form metastasis, although some pathologists believe that metastasis may occur.

Göbell, in 1901, collected 101 cases of retroperitoneal tumors from the literature; 32 were malignant, 43 solid benign, and 26 cystic benign. These cases were apparently not collected consecutively, so that the relative proportion of benign to malignant is probably not accurate. Two of the five myomas were included in this collection.

Mauclaire, in 1910, gave the following list of types of tumors that may occur in the retroperitoneal space:

1. Lipoma, pure.
2. Fibroma, pure.
3. Myxoma.
4. Chondroma.
5. Myoma.
6. Neuroma.
7. Sarcoma.
8. Lymphadenoma.
9. All varieties of cysts.

The origin of retroperitoneal tumors is at best a matter of speculation. All types of tissue in the retroperitoneal space may at any moment develop abnormal growth. The differential diagnosis of these tumors is very difficult; the process of exclu-

sion seems to be the best method of arriving at the correct diagnosis, which is so rarely made.

The records of the Mayo Clinic show that 73 patients with non-metastatic retroperitoneal tumors were observed from January, 1907 to September 15, 1919; 53 of these were operated on; 29 of the tumors were malignant, 18 were benign, and 6 were undetermined.

Fifty-five of the patients were males and 18 were females. It should be stated that the patients who were not operated on were refused operation because the majority had been operated on elsewhere when a diagnosis of an inoperable malignant condition had been made.

The age seems to have practically no influence on the incidence of the disease and type of growths.

Age of patients.	Malignant.	Benign.
0– 5 years	4	1
6–10 "	0	0
11–20 "	1	2
21–30 "	1	1
31–40 "	7	4
41–50 "	7	2
51–60 "	4	7
61–70 "	5	1

In the group of malignant cases were 25 males and 4 females; in the benign were 8 males and 10 females. It will be noted that the incidence in the benign cases was about the same in the males and females, while in the malignant cases the males had the preponderance by more than 5 to 1.

The duration of symptoms was shorter in the malignant cases than in the benign; 21 patients had noted symptoms for less than two years, although 2 had symptoms lasting nine years. The exceedingly long duration in a few of the malignant cases may possibly be explained by the fact that 4 of the sarcomas seemed to have originated from previous lipomas. In the benign cases the duration was, in general, longer, but in the largest single group the duration was less than one year.

The three most prominent symptoms were selected from each case; the tabulation is as follows:

Malignant Tumors.		*Benign Tumors.*	
Loss of weight and strength	20	Abdominal mass	15
Constipation	4	Bloating	1
Abdominal mass	25	Constipation	1
Diarrhea and constipation	1	Abdominal pain	5
Epigastric distress	5	Loss of weight and strength	10
Abdominal pain	10	Increase in size of abdomen	2
Melena	1	Fulness and belching	1
Vomiting	1	Pain in back	2
Testicular pain	2	Paresthesia in right leg, by pressing on growth	1
Pain in thighs	3	Pain in left leg	1
Diarrhea	2		
Night-sweats	1		
Pain in back	1		
Paresthesia in right leg	1		
Pain in bladder region	1		
Abdominal tenderness	1		
Pain in left leg	2		
Frequency in urination	1		
Abdominal gas	1		
Pain in left lumbar region	1		

Since the same symptoms accompany both groups of cases they do not play a part in a differential diagnosis.

Location of the Tumors.

	Malignant.	Benign.
Right upper abdomen	5	1
Right abdomen	4	1
Left upper abdomen	4	4
Right iliac fossa	4	3
Left iliac fossa	4	2
Left abdomen	3	
Epigastrium	1	1
Abdomen	1	3
Abdomen (multiple mass)		1
Above pubis		1
Rectum		1

Location appears to bear no relation to the character of the lesion.

Clinical Diagnosis.

Malignant Tumors.		*Benign Tumors.*	
Tumor of abdomen	5	Malignant retroperitoneal growths	5
Malignant tumor of the right lower quadrant	3	Left abdominal tumor	3
Retroperitoneal sarcoma	3	Benign retroperitoneal growths	3
Tumor of lower right abdomen	2	Tumor of left kidney	2
Left epigastric tumor	1	Epigastric tumor	1
Pyloric ulcer	1	Pyloric ulcer	1
Abdominal tumor (sarcoma)	1	Tumor of the cecum	1
Cystic tumor of abdomen	1	Right-sided abdominal tumor	1
Cyst of the pancreas (infected?)	1	Pelvic tumor (sarcoma?)	1
Tumor of upper right abdomen	1		
Tumor of the upper left abdomen (spleen?)	1		
Tumor of the spleen	1		
Tumor of the upper left abdomen (pancreas?)	1		
Tumor of the left kidney	1		
Large malignant abdominal tumor	1		
Pelvic abdominal tumor	1		
Sarcoma	1		
Sarcoma of the left ileum	1		
Carcinoma of the cecum	1		
No diagnosis made	1		

The clinical diagnosis was correct in 3 of the malignant cases, 2 retroperitoneal sarcomas, and 1 sarcoma of the left ileum. The 3 "benign retroperitoneal growths" were the only correct diagnoses in the benign cases.

Histologic and Operative Diagnosis of Tumors.

Malignant.		*Benign.*	
Sarcoma arising from lipoma	4	Lipoma	5
Round-cell sarcoma	4	Inflammatory mass	2
Sarcoma (operative)	4	Fibromyoma	2
Spindle-cell sarcoma	4	Lymphadenitis with dilatation of lymph vessels	1
Lymphosarcoma	2	Chylous cyst	1
Fibrosarcoma	2	Teratoma	1
Mixed-cell sarcoma	2	Teratoma (operative)	1
Malignancy	2	Fibrolipoma	1
Sarcoma	1	Fibroma	1
Carcinoma	1	Blood-clot	1
Hemorrhagic carcinomatous cyst	1	Fibro- and myxomatous lipoma	1
Fibroblastoma	1	Fibromyxoma	1
Hypernephroma	1		

In making the pathologic diagnosis such conditions as appendical abscess or extension abscess from gonorrheal epididymitis, syphilomas, and tuberculomas were not included; they must be considered, however, in making a clinical diagnosis of retroperitoneal masses.

CONCLUSIONS

In attempting to make a correct diagnosis in cases of retroperitoneal tumors it should first be determined that the mass is retroperitoneal. This may be accomplished in a fairly large percentage of cases by the exclusion of individual organs that are anatomically related to the growth, by means of the cystoscope, the *x*-ray, and the method of inflating the abdominal cavity with oxygen, and then raying. Having decided that the growth is retroperitoneal, it is necessary to decide whether it is benign or malignant.

In the cases observed at the clinic the malignant growths were much more frequent in males than in females. The malignant cases, as a rule, are of shorter duration, and when advanced the patients present symptoms characteristic of malignancy. Such symptoms rarely develop from the pressure which ultimately proves fatal in the benign cases.

A plea is made for exploratory operation in all cases of nonmetastatic retroperitoneal tumors. These tumors must be examined microscopically as well as macroscopically before their pathologic nature can be determined.

BIBLIOGRAPHY

1. Fiori, P.: Contributo alla conoscenza dei tumori retroperitoneali, Policlinico, sez. chir., xi, 550–568, November, 1904.
2. Göbell, R.: Zur Kenntnis der lateral-retroperitonealen Tumoren, Deutsch. Ztschr. f. Chir., lxi, 1–92, September, 1901.
3. Lockwood: Quoted by Douglas, R.: A Study of Retroperitoneal Neoplasms with Special Reference to Diagnosis, Jour. Amer. Med. Assoc., xxx, 705–708, March 26, 1898.
4. Mauclaire: Tumeurs rétropéritoneales prévertébrales, Clinique, v, 39–41, 1910.
5. Ogston: The Surgery of the Subperitoneal Tissue, Lancet, ii, 502, August, 15, 1896.

6. Pfannenstiel: Ueber Myome des Dickdarms, Centralbl. f. Gynäk., xxi, 807, 1897.
7. Schlangenhaufer, F.: Myoma teleangiectodes uteri mit reinen Myommetastasen in der Leber und den Lungen, Wien. klin.Wchnschr., xv, 523–525, May 15, 1902.
8. Uchida, T.: Ueber retroperitoneale Tumoren, München, Schaeffer, 48 pp., 1912.

THE TREATMENT OF CARCINOMA OF THE UTERUS BY RADIUM

LEDA J. STACY, M. D.

THE use of radium in the treatment of malignancy of the cervix uteri at the Mayo Clinic has been confined to inoperable cases: (1) Cases in which the cervix is short and has a deep crater, (2) cases in which the growth has extended on to the vaginal portion of the cervix, and (3) cases in which the broad ligaments are found to be thickened on rectal examination. Radium should be used postoperatively in all cases of pelvic carcinoma, together with deep *x*-ray treatment, cross-firing over the abdomen and back. While it is too soon to determine whether or not the incidence of recurrence is lessened by this measure, the patient should nevertheless have the benefit of its possible advantages.

In 169 cases of carcinoma of the uterus treated at the Mayo Clinic from August, 1915, to January, 1918, there were 79 inoperable cases in which the application of radium or radium and *x*-ray were the only treatments used. In 70 of these the cervix was invaded and in 9 the fundus. Information has been obtained concerning 52 of the 79 patients; 13 (25 per cent.) are still living, 6 for more than two years, and 7 for from one and one-quarter to one and two-thirds years. Of the 39 patients who died, 3 lived from two to two and one-third years, 8 lived from one to one and three-fourths years, and 6 lived from eight to ten months.

Twenty-four patients were treated for recurrence in the vagina or in the deep glands. Information has been obtained concerning 16 of these; only 3 are living, but they have lived two and three years, and two are clinically cured. One has recently been operated on (one and one-half years after the last radium treatment) for the repair of a vesicovaginal fistula, and no evidence of malignancy was found.

In the series of 169 patients, 39 (23.07 per cent.) are living; 1 died of hemorrhage three days after treatment. Two have

lived more than three years, 17 have lived from two to two and three-fourths years, and 5 have lived from one and one-half to one and three-fourths years; all of these report being in "good health." Nine patients of the 39 report that they are in "fair health" one and one-half to two and one-half years after beginning the treatment, and 5 that they are in "poor health" one and one-half to two years after beginning the treatment.

Microscopic diagnosis of epithelioma was made in 64 per cent. of the 169 cases. Cases in which the cancer has extended to the broad ligaments are the least favorable, since the radium rays do not penetrate to a sufficient depth to destroy the outlying carcinoma cells. In practically all cases, however, temporary relief is afforded; the foul discharge ceases entirely or is greatly lessened, and the bleeding stops.

The use of radium is not free from unfortunate complications, the most serious of which are the vesicovaginal and rectovaginal fistulæ. In our series of 79 cases in which radium only was given vesicovaginal fistulæ followed in two instances and rectovaginal fistulæ in two. The immediate reaction following the radium treatment may be rather severe in the cachectic patient with a large ulcerating growth of the cervix. In these cases it is our custom to give only a small dose at the first treatment, using 50 mg. for eight hours; if the reaction is slight, the second treatment is prolonged to twelve hours, and the third to fourteen hours. If nausea and vomiting occur following a treatment, it is not repeated until all symptoms have subsided.

In the routine treatment a series is given once in from three to four months; it consists of three applications for twelve to fourteen hours at intervals of from three to four days of 50 mg. of radium element into the vagina or cervix, if it is possible to insert the tube of radium into the cervical canal. In most cases three applications of radium of 50 mg. for two hours each, at intervals of from two to three days, are made into the rectum, thus cross-firing into the deep iliac and sacral lymphatics. Deep *x*-ray treatments cross-firing over the abdomen and back are given in conjunction with the radium. Brass and lead filters are used and as much gauze packing as is possible for protection.

RADIUM THERAPY IN CANCER OF THE PROSTATE

H. C. Bumpus, M. D.

"In cancer of the prostate the curative treatment by operation is in truth illusory; it is dangerous and gives the most temporary result," Pasteau wrote more than ten years ago. Because of this fact he used radium irradiations, for the first time in 1911, in inoperable cases of the prostate with such satisfactory results that its use has remained the accepted therapy and has replaced surgery in all but a few selected cases.

At first radium was applied through the urethra because its anatomic relationship offered close proximity to the growth, but in well-advanced cases the necessary large enough doses resulted in local burns from the irritating beta rays. Cross-firing was, therefore, attempted by giving half the dosage rectally. The rectal mucosa, however, proved to be even more susceptible to burns than the urethra, and great care was necessary in screening and in regulating the time of exposure in order to prevent such burns, with subsequent cicatricial changes and stricture formation. To overcome these difficulties Barringer, in 1915, placed some radium in a hollow needle and, guided by a finger in the rectum, inserted the radium directly into the gland through the perineum. In this way large doses could be given over considerable lengths of time without producing burns and with the total dosage of the radium going directly into the neoplasm. Since then several modifications of Barringer's method have been used, such as multiplying the number of needles in order to radiate a greater area, substituting radium emanations for the radium salt itself, and leaving capillary tubes of emanations permanently in the neoplasm. A combination of surgery with radium needles has been advocated, the gland being exposed both suprapubically and perineally, and its surface studded with

multiple radium needles of small dosage, which are later removed through the wound by means of strings attached to them.

The several methods described have been used in our clinic. When it is remembered that the dosage of irradiation which any part of the growth receives is in inverse proportion to the square of its distance from the tube, it is evident that the needles which bring the radium in closest apposition offer the most ideal method of application. However, they should be used in conjunction with the other and older methods of rectal and urethral applications, for the latter make possible the application of the rays directly to the periphery of the gland which is the tissue receiving the least amount of dosage from the needles. The clinical bearing of this fact is illustrated by a number of patients who had received treatment by needles alone and still complained of the rectal pain characteristic of carcinoma of the prostate, and who, after having been given one application by rectum, were completely relieved, as well as by the number of "three-year cures" that have occurred when only rectal applications were used. The possibility of diagnostic error following such applications must always be borne in mind, however, for the surface of the gland often becomes much softened, and not until needles are inserted are the characteristic stony masses of carcinoma, that were formerly very easily felt on the surface, made evident by the resistance offered the needles.

We employ four needles in our radium therapy for carcinoma of the prostate, the combined strength of which is about 50 mg. These are inserted through the perineum, two on each side of the midline, and allowed to remain in the gland about twelve hours. Before the needles are applied the patient is placed crosswise on the bed in which he is to remain during the treatment, his feet resting on the arms of the physician's chair, the knees apart, and the legs flexed. The patient retracts the scrotum from the field of operation with his hands, while the physician anesthetizes the perineum which an attendant has first made surgically clean. In anesthetizing, after the skin has been infiltrated, the hypodermic needle is thrust deep in, close to the inner margin of the spine of the ischium, and the pudic nerve is

infiltrated. This nerve supplies the greater portion of the perineum, and on the ability to anesthetize it successfully depends not alone the ease of procedure in accurately applying the needles, but also the patient's complete freedom from pain. After allowing time for complete anesthesia, the left forefinger is inserted in the rectum and the general contour of the growth ascertained. With the right hand the needles are then plunged through the perineum in a downward direction until their tips are felt through the rectal mucosa, when, by a slight upward thrust they are made to enter the gland substance at the desired points. Safety-pins are placed through the eyes of the inserted needles to insure against their loss under the skin. An opium and belladonna suppository is inserted to allay any subsequent discomfort as the cocain wears off, and the patient is placed in bed in the usual position. The needles are left in position for approximately twelve hours, giving a dosage of about 600 mg. hours.

After the localized reaction due to the insertion of the needles has subsided the patient is given rectal treatment. This consists in applying a 50 mg. tube of radium directly over the prostate. Many ingenious mechanical instruments have been devised to hold the radium in the proper position in the rectum. The great majority of such apparatus consists in an arm attached to the examining table which holds in place a metal tube containing the radium. We have found, however, that a piece of sheet lead cut in the shape of a spoon is the most satisfactory applicator. The small metal container holding the radium is placed in the bowl and the lead is bent over three sides of it. Over this a brass tube is slipped to filter the beta rays on the exposed side; the rectal mucosa is, therefore, screened by lead on all sides except directly over the prostatic area, and there the irritating rays are filtered out by the brass tube. After the applicator is inserted and placed in the desired position, with the open side of the bowl next to the prostate, the handle is bent at right angles and attached to the thighs or buttocks by surgeon's plaster. This method allows the patient to move about freely while recumbent and while the applicator is still in position, thus doing away with the discomfort necessitated by remaining

on an examining table to which a rigid mechanical arm is attached. The radium is left in position for a time sufficient to assure a total dosage of 200 mg. hours. When it is possible to do so without causing trauma in cases in which the growth has not obstructed the urethra the patient is also given 200 mg. hours in the prostatic urethra, the radium being inserted by means of a soft-rubber catheter; the gland receives in all 1000 mg. hours. This method has been adopted as the result of our experience during the past three years, and we believe that it gives the best results because of the greatest dosage to the greatest area.

When patients show low kidney function, as determined by the phenolsulphonephthalein test at the first examination, and a high blood-urea, together with considerable residual urine, suprapubic drainage is established and the treatment becomes identical to that of patients being prepared for prostatectomy. If the gland appears to have responded favorably to the radium application and the general condition has improved sufficiently to warrant it, a partial prostatectomy is done; enough of the gland is removed to permit of freely emptying the bladder and doing away with the suprapubic drainage. The percentage of such cases is low, since a considerable number of patients either have but little residual urine, which disappears as a result of the shrinkage of the gland following the radium treatment, or the growth is so extensive, the impairment of general health so marked, and age so advanced that any surgical procedure is absolutely contraindicated.

During 1916, 16 patients with carcinoma of the prostate were treated at the clinic by rectal applications; one of the patients had previously been operated on elsewhere and came to us because of recurrence. Twelve of the 16 patients have been traced; 3 are living, 1 died during the first year, 3 died during the second, 4 during the third, and 1 during the fourth, giving an average life expectancy following the first radium treatment of twenty-six months. These patients received an average dosage of 200 mg. hours, given rectally in two series of treatment of 1000 each. The 1000 mg. hours were given over a period of

about one month, 100 being the greatest dosage applied at one time.

We had the opportunity to examine the gland some months following treatment in 8 of the 16 cases. In all but 2 of these a decrease in size was noted. Five patients reported complete absence of rectal pain following radium treatment, and the majority reported a decrease of pain. This cessation of pain characteristic in carcinoma of the prostate has been noted in the greater number of cases in which radium treatment has been given during the past four years. Five of the 16 patients reported ability to pass a freer stream, and 7 reported marked general improvement, while in 4 there was a rapid decline.

A much larger series of cases has been treated since 1916, but as carcinoma of the prostate is very slow of growth and still slower to metastasize, it is difficult to draw conclusions until at least three years have passed. This series of 16 cases was treated by the old method of rectal application alone. In the later cases in which the improved technic was employed results would naturally be better. The series shows, however, that when radium is not obtainable in needles its rectal application, properly screened, is probably nearly as efficacious, only greater time is necessary for its application, as smaller doses must necessarily be given at each treatment. In order to handle such cases successfully the patients must remain under observation or they must return at lengthening intervals during their lives so that any recurrence may be aborted quickly. It is our practice to have patients return every three months during the first year; after that, once in six months.

From careful perusal of the correspondence of this series of patients and their histories and from physical examinations made at subsequent visits it seems justifiable to conclude that:

1. Radium relieves the intense rectal pain characteristic of prostatic carcinoma in many cases.

2. Radium reduces the size of the carcinoma and delays its growth in the majority of cases.

3. Radium therapy prolongs life in many cases, and possibly completely inhibits further growth of the neoplasm in a few.

BIBLIOGRAPHY

1. Barringer, B. S.: The Treatment by Radium of Carcinoma of the Prostate and Bladder. Preliminary Report, Jour. Amer. Med. Assoc., lxvii, 1442–1445, November 11, 1916. Radium in the Treatment of Carcinoma of the Bladder and Prostate. Review of one year's work. Jour. Amer. Med. Assoc., lxviii, 1227–1230, April 28, 1917.
2. Pasteau, O., and Degrais: The Radium Treatment of Cancer of the Prostate, Arch. Roentgen. Ray, xviii, 396–410, April, 1910.

RENAL ABSORPTION WITH PARTICULAR REFERENCE TO PYELOGRAPHIC MEDIUMS

E. H. WELD, M. D.

THIS study concerning the absorption of different substances from the kidney pelvis was originally undertaken for the purpose of determining, first, the effect of different substances used in pyelography on the kidney tissue, and second, the gradual development of a hydronephrosis as demonstrated by means of the *x*-ray.

The dangers of pyelography have been thoroughly discussed in the literature of the last ten years. Braasch and Mann (1916), in a study of the various substances used in pyelography, give valuable data well supported by experimental work on the effect of all substances used up to that time. Since then Cameron has brought out the use of potassium and sodium iodid as an opaque medium when used in pyelography. In a later article on the same subject Cameron and Grandy further advocate the use of this medium. In 1918 I investigated the advisibility of using sodium bromid for pyelography; my findings at that time suggested the desirability of studying the effects of the newer pyelographic mediums on the kidney.

All the dangers incident to pyelography have resulted from: (1) The use of insoluble mediums, (2) the use of mediums which are poisonous when absorbed, and (3) the injection of the mediums under too great pressure. That pyelographic mediums may reach the circulation is well known to all investigators. The literature is filled with reports on the use and danger of silver substances. The means by which these substances are conveyed to the circulation has not been definitely determined,

and it seems that nothing has been published concerning the absorption from the kidney pelvis.[1]

The questions that have developed in the course of this work are:

1. Is it possible to note the gradual development of a hydronephrosis by means of successive *x*-ray examinations?
2. How long are pyelographic mediums retained in the kidney pelvis?
3. What are the effects of retention of pyelographic mediums?
4. Are pyelographic mediums or other substances absorbed from the kidney pelvis, and, if so, in what manner?
5. Do hydronephrotic kidneys allow any absorption from their dilated pelves?
6. Will substances in the blood-stream or in the intestinal tract enter the pelvis of a kidney which has a ligated ureter with or without a hydronephrotic sac?
7. By what channels does absorption from the blood-stream into the kidney pelvis or from the kidney pelvis into the blood-stream take place?

TECHNIC

Dogs were used in all the experiments. The animal was anesthetized with ether and a lumbar incision was made by the usual surgical technic. The operation seemed to be facilitated if the lumbar region was elevated by means of a pad about 3 inches thick; this gave better exposure. The muscles were split

[1] When this research work was practically completed Burns and Schwartz published an article on absorption from the renal pelves in hydronephroses due to permanent and complete occlusion of the ureter. Because they found India-ink that had been injected into the pelvis in the glomeruli and tubules, they state that "the path of absorption is by way of the tubules and through the capillaries of the glomeruli." They also state that they found India-ink in the glomeruli of the opposite kidney as well as in the spleen and liver. We have repeated this experiment with similar results, but do not believe that the authors are justified in their conclusion that the path of absorption is by way of the tubules to the glomeruli because the India-ink is also found in the glomeruli of the opposite kidney; this proves that the ink was in the circulation, and if it gets into the glomeruli of one kidney by way of the circulation, it may also get into the glomeruli of the injected kidney by the same route. This, however, is a point that is not definitely settled.

down to the peritoneum, which was pushed forward; the ureter was located, drawn up, and ligated, care being taken not to disturb the blood-supply. The various solutions to be tested were then injected into the ureter, which was again ligated about 1 to 2 cm. below the pelvis of the kidney. The ureter was divided between the two ligations. The wound was then closed and *x*-rays taken immediately afterward and at various intervals as long as any shadow of the kidney pelvis could be noted.

The solutions were injected with a piston syringe. As a rule, from 1.5 to 2 c.c. were injected. It is known that this amount of fluid will penetrate somewhat into the tubules and that it will probably cause greater distention than if only enough to fill the kidney pelvis is used. As the same amount of all mediums was injected, however, it was thought that they could be easily compared by this method, even though the pressure was greater than would normally occur in pyelographic work. Furthermore, in ligating the ureter[1] we were not working under normal conditions. Nephrectomies were done on the animals at intervals of from one hour to thirty days and the specimens were studied microscopically. A few of the kidneys were removed at necropsy when the dogs died of intercurrent disease. A number of the kidneys were tested physiologically for the urinary secretory pressure and for absorption, and others were used in perfusion experiments.

The Gradual Development of Hydronephrosis Observed by Means of the *x*-Ray.—In one series of dogs a 25 per cent. solution of potassium iodid was injected in the kidney pelvis, in a second series a 25 per cent. solution of sodium bromid, and in a third series a 15 per cent. solution of thorium nitrate was injected, and the ureter ligated below the point of injection. An *x*-ray was immediately taken, followed by a second *x*-ray in twenty-four hours, when it was found that the shadow had entirely disappeared. Further experiments showed that a shadow was only faintly present one hour after injection and that it was entirely

[1] In another series of experiments the effect of these mediums will be studied under a constant known pressure of injection without the ligation of the ureter.

absent in one and a half hours. The shadow of thorium nitrate was slightly more distinct in one hour than that of sodium bromid or potassium iodid. Saturated solutions of sodium bromid and potassium iodid disappeared in approximately the same time. An insoluble medium such as colloidal silver solution of 25 per cent. was very indistinct two hours after injection. Insoluble substances, such as bismuth carbonate and barium sulphate, stayed indefinitly in the kidney pelvis, however, but they had a tendency to settle in lumps, so that a distinct outline of the kidney pelvis could not be well determined, as the hydronephrosis developed.

In view of the fact that the pyelographic mediums are so readily absorbed, it does not seem practical to watch the gradual development of a hydronephrosis by means of the *x*-ray when the ureter has been ligated.

The Effects of the Retention of Pyelographic Mediums.—The substances tested[1] were a saturated solution of sodium bromid and potassium iodid, a 25 per cent. solution of sodium bromid and potassium iodid, a 15 per cent. solution of thorium nitrate, a 5 per cent. silver iodid emulsion, a 25 per cent. colloidal silver solution, and a 25 per cent. protargol solution; 1½ to 2 c.c. of these different mediums were injected into the kidney pelvis by the usual technic, and at first the kidneys were removed in from five to thirty days after the injection. They were all hydronephrotic, as was shown by gross and microscopic examination. A few of them were infected. The tissue showed, mainly, the effects of gradually developing hydronephrosis apparently identical to that in the tissue obtained when the ureter was ligated without the injection of any substance into the kidney pelvis. When a nephrectomy was done one to three hours after the injection and ligation the medullary tissue was congested and reddened. Microscopically, the medullary portion showed an acute congestion, while the cortical portion was normal. This area of congestion is better shown when methyl-

[1] Since all but the newer pyelographic mediums had been tested by Braasch and Mann, the main emphasis of the study was made on those mediums which are soluble.

ene-blue, eosin, or colliodal silver (Fig. 146) are injected into the kidney pelvis, for these materials stain only the medullary portion, especially at the poles of the kidney. The unabsorbable

Fig. 146.—Injection of kidney pelvis with methylene-blue at 40 mm. mercurial pressure while the circulation was still intact. Nephrectomy ten minutes later.

mediums, such as colloidal silver, are apt to produce areas of cortical necrosis; silver iodid effects the tubules much more than it does the glomeruli. This is possibly owing to the fact that the silver emulsion does not reach the glomeruli, but stays in the

tubules of the medullary portion. It is noticeable that in all experiments very little effect was produced in the glomeruli, even when the tubules were almost totally destroyed. All substances used in pyelography, when retained, will, in a certain percentage of cases, produce a pyonephrosis. This will also occur occasionally when the ureter is only ligated and when no injection is made, a fact always to be taken into consideration in studying the effects of different pyelographic mediums. It is apparent that in experiments to determine the effect of pyelographic mediums on kidney tissue too long a time elapsed after the injection of the medium into the kidney pelvis before the nephrectomy was done because the medium soon leaves the kidney, as is shown by *x*-ray. Any damage will be shown in an acute condition one or two hours after the injection.

The damage that is found when the kidney is taken out five or six days after the injection has been made is probably due largely to the effect of the gradually developing hydronephrosis, unless, of course, an unabsorbable medium has been used. From the standpoint of effect on the kidney tissues little if any difference will be found between the newer pyelographic mediums, sodium bromid, potassium iodid, and thorium nitrate.

Experiments to determine the toxicity of the different substances have given surprising results. Inasmuch as it has not been known that pyelographic mediums could be absorbed rapidly, very little attention has been given to their toxic effects. In view of the knowledge gained from the experiments, however, it seemed advisable to test the toxicity of the substances. The results of this investigation are given in detail in another paper.[8] Briefly, it was found that sodium bromid and sodium iodid are apparently innocuous when injected intravenously in large doses. Potassium iodid is very toxic, due to the potassium ion. Thorium varies in its toxicity. The solution taken from some bottles was very toxic, while that from other bottles was inert.

The Absorption of Different Substances by the Kidney.—In order to ascertain how soon substances will absorb, phenolsulphonephthalein, sodium bromid, potassium iodid, and brilliant green solutions were injected into the kidney pelvis and the

ureter was ligated. These substances were found in the opposite ureter in from six to twelve minutes. When there was a rapid diuresis the substances came through more quickly. In one representative experiment a tube of phenolsulphonephthalein 4 mm. in diameter and 370 mm. in height was connected to the right ureter. In five minutes this pressure dropped to 290 mm., showing that there had been considerable absorption. The dye came through from the left ureter six minutes after it had entered the right ureter. At 290 mm. pressure it remained stationary for ten minutes, showing that this apparently was the secretory pressure of the kidney. From these experiments I conclude that substances are very rapidly absorbed by the kidney from the kidney pelvis. Phenolsulphonephthalein is taken into the circulation from the kidney pelvis just as rapidly as if it were given by intramuscular injection. The advantage of using non-toxic pyelographic mediums is demonstrated.

Excretion into the Pelvis of a Hydronephrotic Kidney, and Absorption from the Pelvis in Such a Kidney Produced by Ligation of the Ureter.—Phenolsulphonephthalein and potassium iodid were injected into the stump of the ureter of hydronephrotic kidneys and the ureter was ligated at the point of injection. It was shown that these substances were absorbed and then excreted by the other kidney. The rapidity of this absorption apparently depends on the amount of medullary tissue that remains in the hydronephrotic kidney, or, the larger the hydronephrotic sac, the less the medullary tissue and the slower the absorption. It was found that when these substances were fed to dogs or injected into the jugular vein they could easily be seen in a normal kidney pelvis with a ligated ureter or in a hydronephrotic sac. The amount varied in inverse proportion to the size of the hydronephrosis that had developed.

A typical example of absorption into or from a hydronephrotic sac is given in the following experiments:

Excretion into a Hydronephrotic Sac.—Experiment 123—19. Dog D19. Ligation and division of the left ureter. Sixteen days later, injection of 2 c.c. of phenolsulphonephthalein into the jugular vein. Four hours later a nephrectomy was done. A

hydronephrosis of 40 c.c. capacity contained a trace of phenolsulphonephthalein. The bladder urine gave 22 per cent. phenolsulphonephthalein return.

Absorption from a Hydronephrotic Sac.—Experiment 121—19. Dog D17. Ligation and division of the left ureter. Sixteen days later, injection of 1.5 c.c. phenolsulphonephthalein into the left hydronephrotic kidney. Forty-two hours after the injection the dog excreted 95 c.c. of urine which contained 20 per cent. phenolsulphonephthalein. Seventy-two hours after injection a left nephrectomy was done. A hydronephrosis of 55 c.c. capacity contained 30 per cent. phenolsulphonephthalein.

These experiments seem to show that there is a circulation or transference of absorbable drugs into and out of the kidney pelvis when the ureter is ligated, and that this is greater in proportion to the amount of normal kidney tissue that remains. It is also greater if there is active kidney secretion, such as can be induced by diuretics. It has been said that the size of a hydronephrosis depends on the amount of collateral circulation that develops. I am inclined to believe that the collateral circulation that develops is secondary to the development of a hydronephrosis. It is certainly true that the larger the hydronephrotic sac, the larger the collateral circulation. It seems more likely that the difference in the size of the hydronephrotic sac in a given length of time depends more on the activity of the secretion of the kidney than on the amount of collateral circulation developed, for the greater the diuresis, the larger the secretory pressure and the greater the dilatation of the pelvis of the kidney. It was found that with a secretory urine pressure of 600 mm. the injection of 100 c.c. of a 2 per cent. solution sodium sulphate intravenously caused the secretory pressure to go up to 1150 mm. of urine pressure, at which it remained stationary for one hour. Two experiments were performed in which $\frac{1}{2}$ c.c. of phenolsulphonephthalein was injected into a ureter which had been ligated at its juncture with the kidney pelvis and just before it entered the bladder. In these experiments no absorption of phenolsulphonephthalein was noted in the four days that the animals were kept under observation.

Channels through which Substances in the Blood-stream Enter the Kidney Pelvis or Enter the Blood-stream from the Kidney Pelvis.—In order to ascertain how this absorption could take place several experiments were undertaken; Locke's solution was used as a perfusion medium. The kidneys were removed from an anesthetized dog; they were kept moist and warm while cannulas were placed in the ureter, vein, and artery; they were then perfused with Locke's solution at body temperature. The artery was perfused first so as to be sure of washing the blood from the kidney. Further precaution was taken to clamp the artery before the vein when the kidney was removed from the living animal. Mann has frequently noted and found experimentally that the kidney cannot be perfused backward, that is, from the vein to the artery. The kidney becomes tense and hard and does not allow any fluid to come from the artery when as much as 120 mm. mercury pressure is used on the vein. Occasionally, however, a very small amount comes from the ureter. We know that most organs, such as the spleen, the thyroid, or an extremity, can have a reversed circulation, that is, an anastomosis may be made between an artery and a vein and also between a vein and an artery, and the part will live. In the kidney, however, no fluid will come from the vein out of the artery even when 150 mm. mercury pressure is used. It seems possible that the double capillary system which exists here may be responsible for the phenomenon, and it may be that the obstruction made in the first capillary network dilates the tubules on the second network so that they are closed. In this way a valve action exists that effectively stops the flow. When the artery was connected with the Locke solution of 100 mm. pressure the solution dropped very rapidly from the vein, and a slight amount from the ureter. If the vein was slightly constricted it dropped more rapidly from the ureter.

After the blood had been washed from the kidney by perfusion through the artery, the ureter was connected with Locke's solution under pressure, and it was found that it would go through the vein fairly rapidly. When the pressure on the ureter was 120 mm. of mercury, the solution came from the vein at a

pressure of 20 mm. of mercury. When the perfusion solution was colored with methylene-blue or brilliant green, it was found that the colors rapidly made their appearance in the fluid from

Fig. 147.—Renal vein injected with potassium chromate solution; renal artery injected with silver nitrate solution. Red silver chromate precipitated in cortical portion.

the vein. When a kidney that had been perfused with methylene-blue solution by the ureter was sectioned longitudinally, it was found that only the medullary portion of the kidney was

stained. This was true whether the solution was injected in the live animal or after the kidney had been removed.

When the vein was injected with the potassium chromate solution and the artery with silver nitrate solution a red pre-

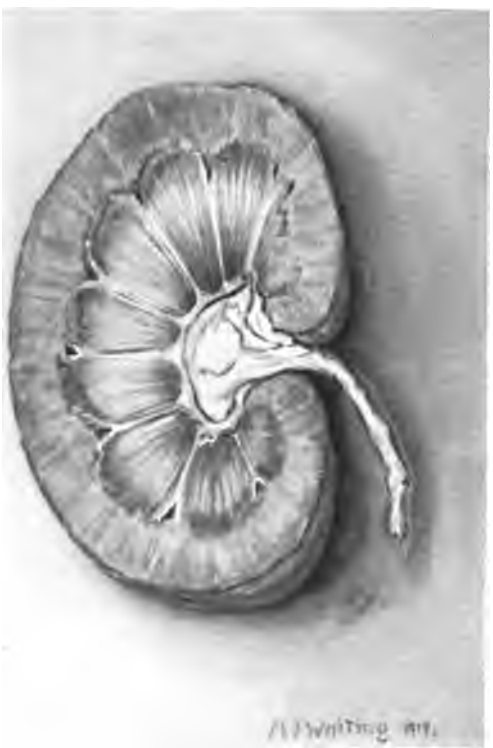


Fig. 148.—Renal vein injected with potassium chromate solution; ureter injected with silver nitrate solution. Red silver chromate precipitated in the medullary portion.

cipitate of silver chromate was produced in the cortex, while the capsule, medullary portion, and pelvis were yellow (Fig. 147).

When silver nitrate solution was injected into the ureter and potassium chromate was injected into the vein, a red precipitate of silver chromate was noted in the medullary portion only (Fig. 148).

From these experiments it is apparent that there is a circulation within the kidney from the artery to the vein, and also the possibility of one from the pelvis to the vein, which are independent of one another. If the venous circulation is injected

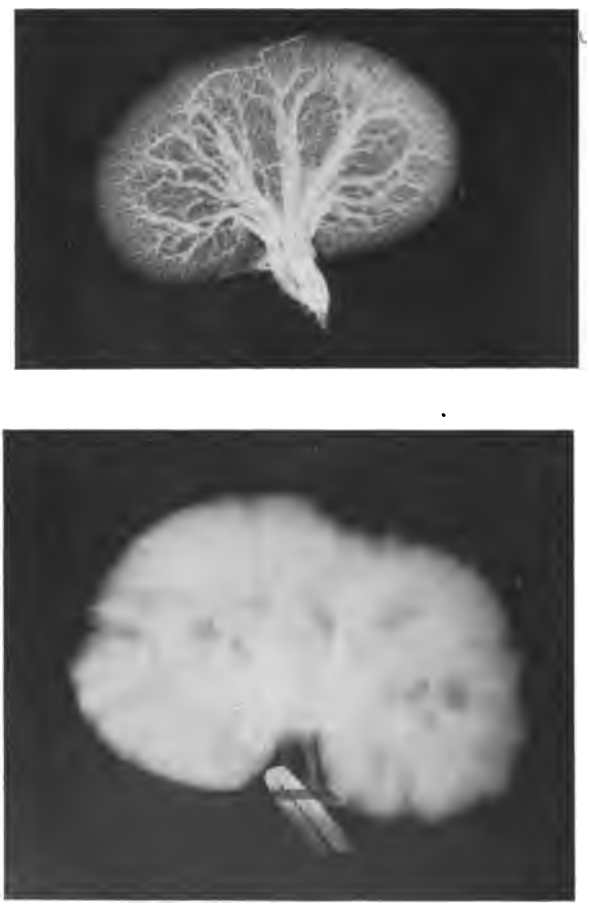
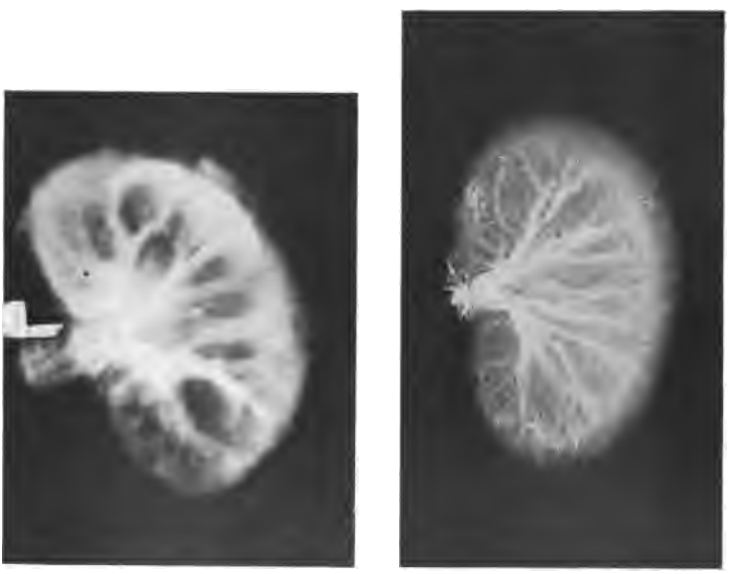


Fig. 149.—Radiograph of an injection of the venous circulation of the kidney: *a*, Sodium bromid solution; *b*, bismuth emulsion with condensed milk.

with an opaque medium (Fig. 149) the whole of the kidney is uniformly injected, the venous radicles apparently being almost equally distributed throughout the cortex and medulla. If the arteries are injected, however, about 90 per cent. of the capillary circulation is in the cortex (Fig. 150). This shows that the

medullary portion of the kidney has a large venous system, but a relatively small arterial system. We might conceive of the circulation in the kidney as represented in Fig. 151. All the fluid enters the kidney through the artery, from which part of it goes through the capillaries of the glomeruli and is then collected into smaller arteries. From this a second set of capillaries springs which surround the tubules, and is then collected into the veins. The other part of the fluid, a serous portion,



a *b*

Fig. 150.—Radiograph of an injection of the arterial circulation of the kidney: *a*, Sodium bromid solution; *b*, bismuth and sodium bromid.

leaves the arterial system at the glomeruli and probably some at the convoluted portion of the tubules. This fluid is said to gain entrance into the tubules probably by physical processes and also by vital activity of the cells. The fluid, so-called glomerulous filtrate, travels down the tubules and is in a large part reabsorbed into the venous circulation either by vital activity of the cells or by physical processes. The part that is not absorbed escapes into the pelvis of the kidney as urine.

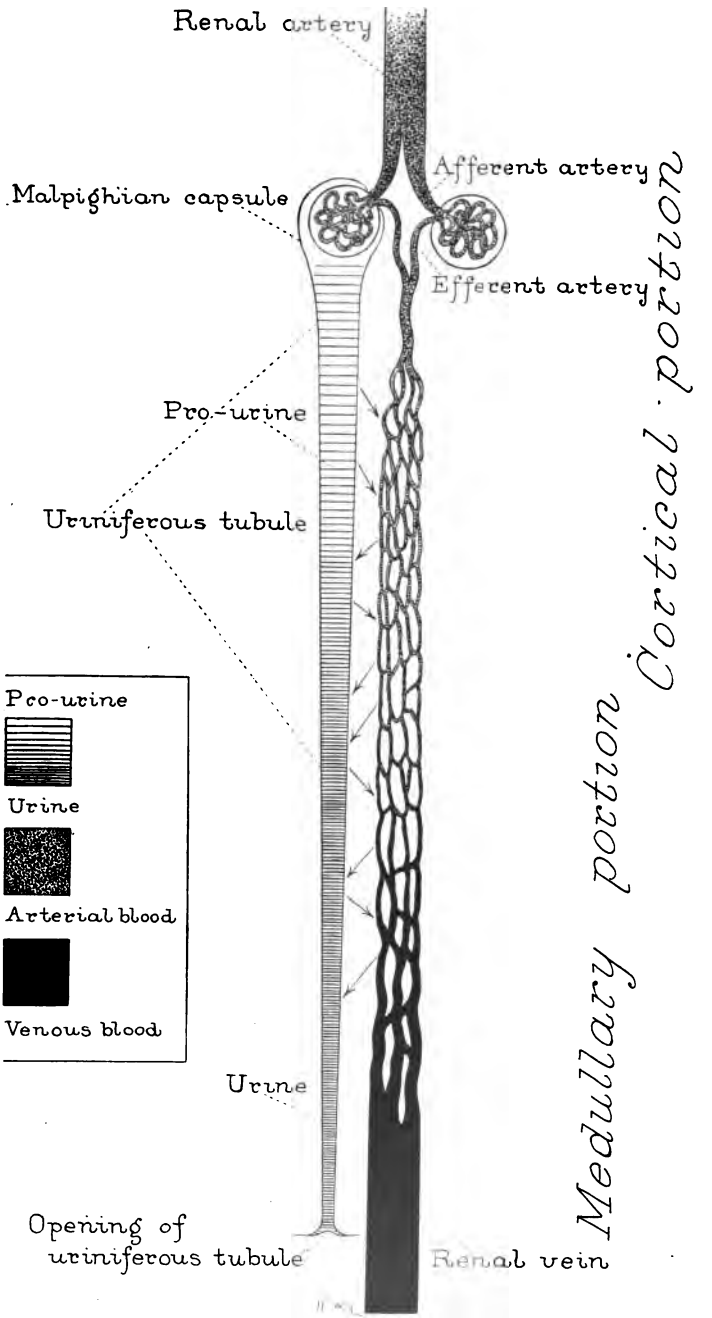


Fig. 151.—A diagrammatic conception of the "modern view" of urinary secretion.

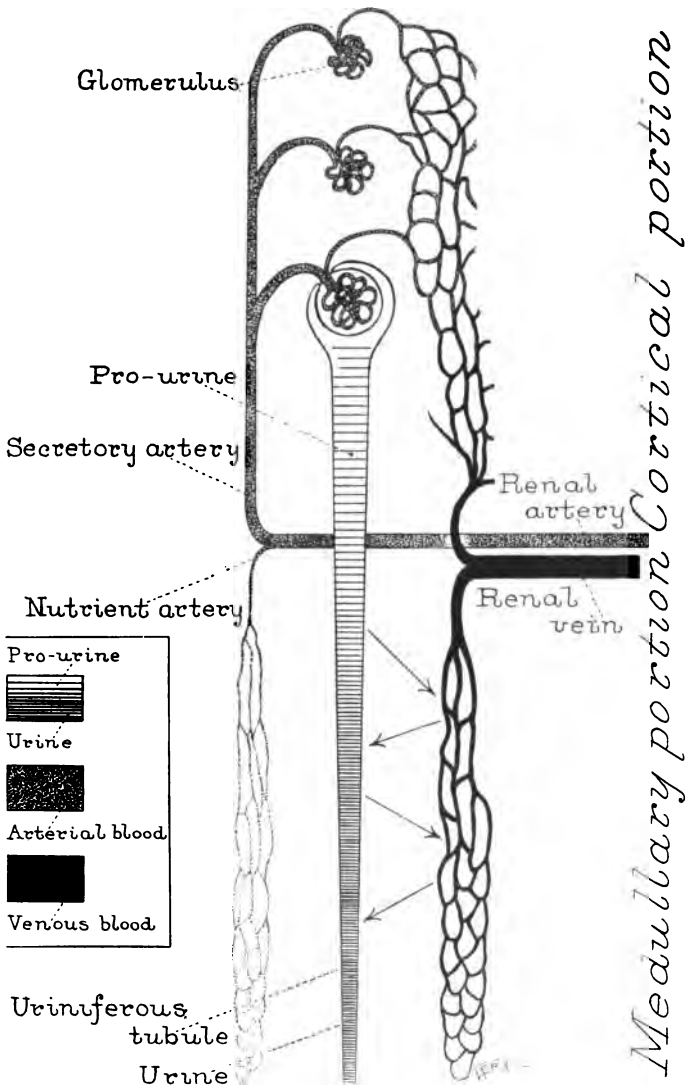


Fig. 152.—Diagram of absorption from the uriniferous tubule and the formation of urine.

Figure 152 illustrates the results that have been deduced from analysis of the experiments; it also shows the probable course of fluid when it is injected into the ureter and escapes from the vein.

If colloidal silver is injected into the vein of a dog it rapidly causes death, as is noted in the blood-pressure tracing (Fig. 153). If colloidal silver is injected into the ureter, however, no effect

Fig. 153.—Collargol injected in vein. (Blood-pressure tracing.)

is noted until the pressure reaches approximately 250 mm. of mercury. If there is a sudden release of pressure the colloidal silver rapidly leaves the syringe and the animal dies (Fig. 154).

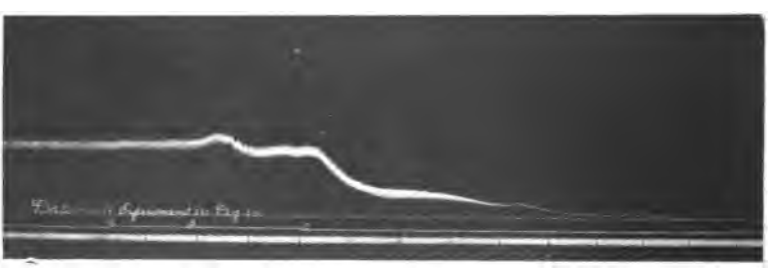


Fig. 154.—Collargol injected in ureter under 250 mm. pressure. (Blood-pressure tracing.)

Apparently the solution breaks through the tubule walls and enters the veins. It is interesting to note that the break always occurs at the poles (Fig. 155). It is surprising how little force one has to exert on the syringe to make a pressure of 250 mm. of

mercury. Death usually occurs four or five minutes after the injection; this undoubtedly explains many of the cases of sudden death after the use of colloidal silver, which are mentioned in the literature. It also emphasizes the necessity of using non-toxic mediums in pyelography and of avoiding too high pressure in making pyelographic injections.

From this experimental review of the absorption and toxicity of the pyelographic mediums it is seen that a very definite advance in pyelography was made when a soluble medium was first suggested by Burns. Another advance was made when

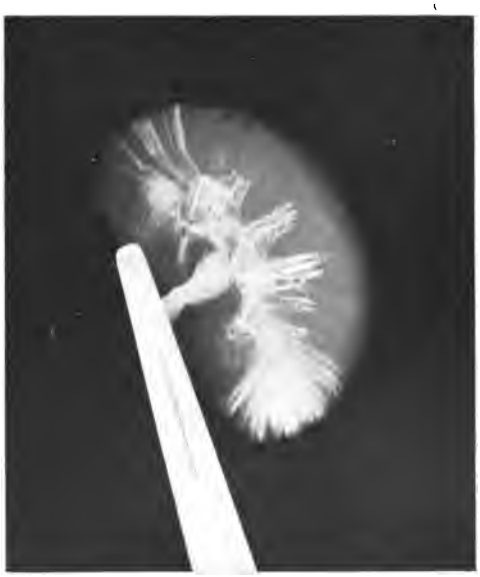


Fig. 155.—Radiograph of an injection into the kidney pelvis. Colloidal silver injected under pressure breaking through at the poles of the kidney.

Cameron and Grandy produced a more simple medium. Sodium bromid and sodium iodid are the best mediums yet advocated, and from the point of efficiency and safety they cannot be equaled by any other mediums.

CONCLUSIONS

1. It is not feasible to note the gradual development of hydronephrosis by *x*-ray.

2. There does not seem to be much difference in the effect on the kidney tissue of retention of the soluble solutions used as pyelographic mediums, sodium bromid, potassium and sodium iodid, or thorium nitrate.

3. Sodium bromid and sodium iodid are seemingly non-toxic when injected directly into the vein.

4. Thorium nitrate 15 per cent. solution as now put on the market varies in toxicity. Some solutions tested have been very toxic.

5. Potassium iodid solutions are very toxic when injected into the veins.

6. The effect on the kidney tissue of a pyelographic medium retained in the kidney pelvis is most noted in the first hour after injection. Later the effects seem to be the same as would occur from the gradual development of a hydronephrosis from a ligated ureter. This is not true when silver salts or other insoluble mediums are used.

7. The soluble mediums, as sodium bromid, potassium and sodium iodid, and thorium nitrate, are not retained in the kidney pelvis more than one and one-half hours when the ureter is ligated, but are absorbed rapidly, apparently from the medullary portion of the kidney.

8. Hydronephrotic kidneys allow absorption from their sacs in inverse proportion to the size of the sac or the amount of kidney destruction. The kidney tissue first to be destroyed is the medullary portion.

9. Substances in the blood-stream or in the intestinal tract enter the pelvis of a kidney with a ligated ureter in inverse proportion to the size of the hydronephrosis that has developed.

10. Absorption from the pelvis seems to take place mainly through the medullary portion of the kidney. Perfusion experiments indicate that this is a very rapid process. The nuclei of some cells are stained when dyes are absorbed; this indicates that the process is more than one of filtration.

11. Absorption from the kidney pelvis indicates that the kidney may be a focus of infection that should always be considered.

12. Unabsorbable mediums produce destruction of the kidney tissue, and should, therefore, not be used.

13. There is danger of injecting pyelographic mediums directly into the blood-stream if too great a pressure is exerted; for this reason non-toxic sterile mediums should be used.

14. Sodium bromid seems to be the most practical pyelographic medium thus far produced.

BIBLIOGRAPHY

1. Braasch, W. F., and Mann, F. C.: Effects of Retention in the Kidney of Media Employed in Pyelography, Amer. Jour. Med. Sci., clii, 336–347, September, 1916.
2. Burns, J. E.: Thorium—a New Agent for Pyelography: Preliminary report, Jour. Amer. Med. Assoc., lxiv, 2126, 2127, June 26, 1915. Further Observations on the Use of Thorium in Pyelography, Jour. Amer. Med. Assoc., lxviii, 533–535, February 17, 1917.
3. Burns, J. E., and Schwartz, C. O.: Absorption from the Renal Pelvis in Hydronephrosis Due to Permanent and Complete Occlusion of the Ureter, Jour. Urol., ii, 445–455, December, 1918.
4. Cameron, D. F.: Aqueous Solutions of Potassium and Sodium Iodids as Opaque Mediums in Roentgenography, Jour. Amer. Med. Assoc., lxx, 754, 755, March 16, 1918.
5. Cameron, D. F., and Grandy, C. C.: Sodium and Potassium Iodids in Roentgenography, Jour. Amer. Med. Assoc., lxx, 1515, 1517, May 25, 1918.
6. Mann, F. C.: Personal communication.
7. Weld, E. H.: The Use of Sodium Bromid in Roentgenography, Jour. Amer. Med., Assoc., lxxi, 1111, 1112, October 5, 1918.
8. Weld, E. H.: The Toxicity of Pyelographic Mediums: Report of a Death Following the Use of Thorium Nitrate, Jour. Urol.

AN INSTANCE OF PRIMARY PORTAL THROMBOSIS

Illustrating a Not Uncommon Source of Diagnostic Error

W. W. BISSELL, M. D.

IN enumerating the causes of various rather common objective manifestations of disease the student of medicine is guided quite rigidly by the limits of his experience in arriving at a definite diagnosis. To be sure, there can be nothing more safe than a wide experience in the taking of clinical histories and recording of objective findings in the routine of diagnostic practice. Recognizing that it is based on such experience that high clinical diagnostic efficiency may be verified by operation or necropsy, it is to be remembered that one's clinical judgment may be biased by an experience possibly too rich in diseases of obscure origin; disorders not common in general practice.

In a very large clinic receiving many patients whose maladies may have been the subject of critical investigation by most competent physicians, resulting in indefinite diagnoses, possibly indicating surgical treatment, it rarely happens that operation may verify a clinical conception of an unusual disorder and yet be in error as demonstrated by postmortem examination. Particularly is this true of the disorders referred to—those uncommon diseases of obscure origin.

The detection of these instances of diagnostic error is one of the reasons for placing a necropsy service in the organization of group-practice of medicine and surgery.

In this connection the following clinical and postmortem résumé of an instance of primary portal thrombosis is of interest.

CASE 181363.—A pale, weak, married woman, thirty-six years old, entered the Mayo Clinic for general examination

December 28, 1916. She brought a note from her physician stating that she was suffering from an enlargement of the spleen with anemia; that abdominal paracentesis within the previous two weeks had relieved her of a large quantity of ascites fluid, which was returning very rapidly; that the blood contained nearly normal numbers of red and white cells and decreased hemoglobin percentage, and that a Wassermann reaction yielded negative results.

Nothing of special importance was elicited in the family and menstrual history. The patient had suffered a miscarriage at the fifth month in 1913. She never used alcoholics and her life was the normal one of a childless housewife. She complained chiefly of weakness, progressive enlargement of the abdomen, and a rather persistent diarrhea. Since 1909 or 1910 she had had the inconvenience of a diarrhea, the attacks of about one month's duration usually of no more than four loose movements a day. She had not noticed blood or mucus in the stool. In 1905 or 1906 she was taken with an abrupt attack of acute abdominal pain, localized rather high up under the costal arch in the midline, accompanied by fever, but not associated with icterus, and, at the time, not thought to be attributable to gall-bladder disease. There was no recurrence of this pain until about 1913, when she suffered a similar attack, which her physician called acute indigestion. The pain was definitely localized in the epigastrium, was accompanied by fever and vomiting, and necessitated the administration of morphin. Since 1913 several similar attacks of pain had always been accompanied by fever and were of such severity that they required the use of morphin for relief. None of these attacks were associated with icterus. During the spring and summer of 1916 she had noticed a progressive enlargement of the abdomen, with increasing weakness and gradual wasting.

Physical examination revealed a somewhat wasted, pale, weak, prematurely aged young woman with a greatly enlarged abdomen. The spleen was easily palpable, filling the left upper abdominal quadrant as low as the level of the umbilicus. That the greater part of the abdominal enlargement was due to ascites

was very certain. After the withdrawal of a large quantity of ascites fluid the liver dulness occupied its normal position and indicated a liver of normal size. The diaphragm was slightly elevated on both sides. There were no physical signs of heart disease and the pulse was of good quality and normal rate. The systolic blood-pressure was 118, the diastolic 78, and the pulse-pressure 90. Nothing abnormal could be found in the urine. Careful examinations of stool samples revealed no parasites. The blood contained 4,000,000 erythrocytes per cubic millimeter, 8800 leukocytes, and 70 per cent. hemoglobin. One differential count revealed 77 per cent. polymorphonuclear neutrophils, 16 per cent. small lymphocytes, 3 per cent. large lymphocytes, 3 per cent. eosinophils, and 0.3 per cent. basophils. There were moderate anisocytosis and poikilocytosis and a slight polychromatophilia.

We were dealing, then, with a young woman suffering a general weakness with anemia, splenomegaly, and ascites. There was no physical basis for the assumption that this whole clinical picture was due to a Laennec cirrhosis of the liver. The blood contained some very meager evidence for the diagnosis of a splenomegaly of obscure origin, possibly splenic anemia. It was difficult to associate the diarrhea with splenic enlargement and ascites. The ascites could not be attributed to a cardiac disorder. The history of the attack of acute abdominal pain with fever in 1905 or 1906 may or may not have been important, but in the light of late (postmortem) observations, perhaps this was the most important item in the history. At least, it might appear that this pain was of similar origin to that of 1913, and the attacks occurring at intervals of a few months up to the time of this consultation. The patient complained of diarrhea rather than of the pain, and it is possible that because of this we allowed our attention to be focused on an effect rather than on a cause. At least, the matter of pain did not seem to be the subject of critical inquiry in the history recorded. When all the clinical data had been gathered the cause of the splenic enlargement and ascites was most obscure. Presented to surgical consultation it was natural that the surgeon's attention was

held by the large spleen. This was the tangible thing which he could remove or for which he could attempt treatment if its enlargement proved to be the result of circulatory disturbance. The patient was losing ground rapidly, and it seemed justifiable to abandon further clinical investigation for laparotomy and surgical judgment. Accordingly, Dr. W. J. Mayo removed the spleen, which he found bound to the diaphragmatic peritoneum by fibrous adhesions. The operation was difficult and attended by considerable blood loss. Exploration of the abdomen revealed no abnormalities other than the splenomegaly and ascites. An attempt at establishing a collateral circulation between the portal and systemic venous circuits did not appear necessary, since there were no liver cirrhosis and no evidence of obstruction in the portal circuit proper.

The patient's weakened condition did not react favorably after operation. She did not complain of pain, although her temperature rose to 103° F. on the second day. Death was asthenic seventy-two hours after operation, with a pulse-rate of 145 and a fever of 104.2° F. Clinically the death was attributed to operation, although postoperative urinary suppression had led an intern to record, "Suppression of urine; uremia."

At necropsy the following anatomic diagnosis was made:

Primary (healed) fibrocalcareous portal thrombosis; (healed) fibrous mural thrombosis of the inferior mesenteric vein; fibrous obliteration of one of the principal tributaries to the superior mesenteric vein; recently formed mottled thrombi in the distal tributaries to the superior mesenteric vein and in the splenic vein; unusually large tortuous splenic vein; marked ascites; moderate general emaciation and anemia; absence of the spleen by very recent splenectomy; large external hemorrhoids; unusually high arching of the diaphragm.

The accompanying illustration, in which Mr. Sweet has accurately replaced the spleen in its normal relation to the necropsy specimen, affords an excellent description of the lesions named in the anatomic diagnosis. The spleen weighed 1480 gm. and contained many healed fibrous and recently formed red hemorrhagic infarcts. Aside from infarction, microscopic

preparations of the splenic pulp revealed nothing more noteworthy than chronic passive hyperemia. In the illustration the cylindric shape of the fibrocalcareous cord in the portal vein is to be noted. This cord is adherent to the anterior wall of the vein. Likewise, the flattened, band-like, healed thrombus of the inferior mesenteric vein is on the anterior wall. If evidence should be needed to justify the naming of this lesion "thrombus," the small bridgings of fibrous tissue, remnants of canalization, in the upper inferior mesenteric vein should be sufficient. The extreme right tributary to the superior mesenteric vein has been completely obliterated at the point indicated just above the widely distended terminal portion filled with black clot.

Without a postmortem examination we might have named "splenic anemia" as the principal cause of death. Our clinical experience had been "too rich," possibly, in the observation of splenomegaly attributable to splenic anemia. At operation nothing was observed to contraindicate a diagnosis of splenic anemia unless it was the presence of a great amount of ascites fluid without cirrhosis of the liver. Aside from this feature, then, the diagnosis was essentially a clinical one.

To return to the interpretation of clinical aspects of the case in relation to the postmortem observations: We at once evaluate the pain, its occurrence in sharp attacks accompanied by fever and requiring the use of morphin for relief, as possibly the essential history item. The initiation of pain had antedated the onset of diarrhea, and, if pain was due to a recurrent thromboulcerative process in the portal vein and its tributaries, it possibly accounts for the diarrhea, since there were but three or four loose bowel movements daily. As to the splenomegaly and ascites without liver cirrhosis, portal thrombosis offers complete explanation.

Our attention was held by the splenomegaly and ascites. Diarrhea was not considered an essential of the history, and the abdominal pain went unaccounted for. The patient needed active treatment if life was to be spared. On the one hand, a successful experience possibly too rich in splenectomy dominated therapeutic considerations; on the other hand, obscure

diagnosis and almost utter hopelessness of medical therapy robbed the clinician of the courage necessary intuitively to insist that treatment was not surgical.

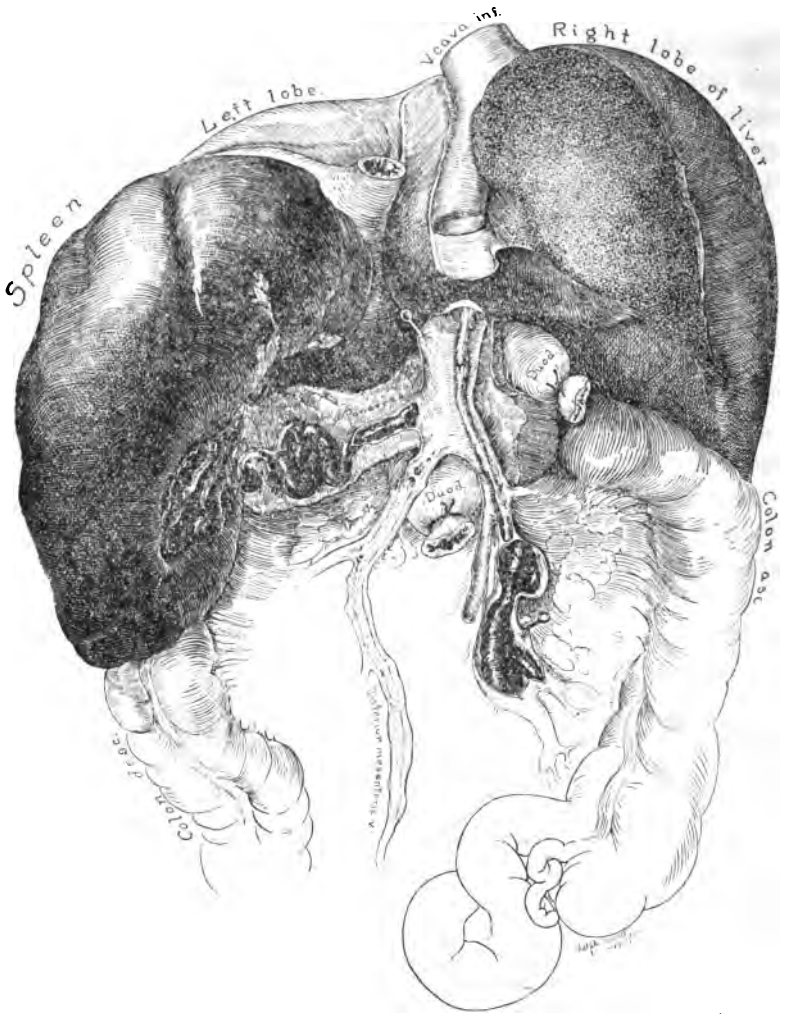


Fig. 156.—An instance of primary portal thrombosis.

It is understood, of course, that splenic anemia in its later stages may resemble portal thrombosis very closely, but in the

diagnosis of the latter we learn from this instance to attach a greater significance to pain.

Finally, it might be intimated that the thrombosis in the portal vein and its tributaries could have been overlooked at postmortem examination. Not uncommonly one may witness a necropsy in which examination of the portal vein is not undertaken. Figure 156 is an accurate reproduction of the portal vein and its relationships as we see it in routinely conducting our examinations from behind after the method employed by Dr. E. R. LeCount.

A REPORT OF FIFTEEN CASES OF ERYTHREMIA

H. E. MARSH, M. D.

ERYTHREMIA, or primary polycythemia, was first described by Vaquez in 1892. He reported a case of peculiar cyanosis with an increase in the number of red blood-cells and splenomegaly, which he attributed to congenital disease of the heart. This patient died three years later, and necropsy revealed the absence of any organic heart lesion. The reports of several cases followed this, but it was not until 1903 that the disease was given prominence by Osler. Lucas, in 1912, was able to collect 149 cases.

Since 1911, 15 cases of erythremia have been observed in the Mayo Clinic. One case is of special interest, inasmuch as the patient has been under observation for three years. The history is as follows:

CASE I (A178054).—A woman aged forty-five was first examined at the clinic November 11, 1916. The patient's family history was unimportant. She had three children living and well. Her menstrual periods had always been regular, but the flow was excessive; the last period had occurred three months before. She had had pleurisy at thirty-eight. For the past eight or ten years she had suffered from severe right temporal and frontal headaches, which had been worse the last three years. The headaches were so severe at times that she was obliged to take an opiate and go to bed; if nothing were done for relief the headache continued for two days. These attacks seemed to follow physical or mental strain and were not associated with nausea or vomiting. Three weeks before her examination she suddenly lost the use of her left arm; the paralysis improved slightly with massage, but a marked weakness of the arm remained.

In her youth the patient had had a florid complexion; this had become marked since the menopause. For three years she had had frequent hot flushes; these intensified the reddish color of her face, as did also exposure to cold. Her bowels were constipated, requiring the daily use of laxatives.

Examination revealed a well-developed and well-nourished woman, with the skin of the face and hands a dark red, and the mucous membrane of the lips a reddish blue. The retinal veins were tortuous. She had a moderate degree of dental caries. The nose and throat examination revealed hypertrophic rhinitis, no adenoids, tonsils moderately enlarged, larynx negative, and antra negative. A few cervical glands were palpable. The heart and lungs were negative; systolic blood-pressure was 170; the diastolic was 110; pulse 92; temperature 98.8° F. There was present a hemiparesis of the left arm, doubtless due to hemorrhage in the right cortical area. The spleen was palpable 2 inches below the left costal margin. The liver extended 1 inch below the right costal margin. On both sides of the abdomen on a level with the umbilicus were movable masses which cystoscopic examination showed to be polycystic kidneys. The Wassermann test was negative. The patient's blood-corpuscles showed an increased resistance to hypo-isotonic salt solution. The urine contained a trace of albumin and a few leukocytes. The combined phenolsulphonephthalein test gave a 55 per cent. return in two hours. The hemoglobin was 88 per cent.; red cells 8,610,000; white cells 10,000. A differential count showed polynuclear neutrophils 77 per cent., small lymphocytes 14 per cent., large lymphocytes 5 per cent., eosinophils 2 per cent., basophils 2 per cent. Coagulation time, seven minutes; bleeding time, three minutes.

November 23, 1916, the patient received a twelve-hour exposure of 100 mg. radium over the spleen. After this the hemoglobin was 83 per cent., red cells 7,520,000, white cells 9600, polynuclear neutrophils 78.3 per cent., small lymphocytes 16 per cent., large lymphocytes 2.3 per cent., eosinophils 3 per cent., basophils 0.3 per cent. The spleen was palpable 1 inch below the costal margin. The patient's color was slightly im-

proved, and she was free from headaches. December 3d a second twelve-hour exposure of 100 mg. radium was made over the spleen. There was no reduction in the size of the spleen and no change in the color of the face; the headaches returned. The hemoglobin rose to 88 per cent., and the red cells dropped to 5,560,000. December 12th the red cells had jumped to 8,900,000.

The next radium treatment, December 16th, was given over the long bones, seven three-hour exposures of 100 mg. The spleen decreased in size, being just palpable under the costal margin. The red cells rose to 9,280,000 following this and the hemoglobin to 90 per cent. One month later the hemoglobin was 90 per cent. and the red cells 8,550,000; white cells, 7200.

In May, 1917, six months after the original examination, the hemoglobin was 98 per cent., the red cells 7,200,000. The patient was next seen September, 1917. She returned on account of weakness and of soreness over the region of the spleen on exertion. Four days before this she had lost her memory for about an hour; the condition came on while she was standing over a hot stove cooking. There had been a marked improvement in the headaches, but the hot flushes came as frequently as formerly. The patient had had nosebleed once since the first examination. The intense reddish color of the face and hands persisted. The spleen was palpable about $\frac{1}{2}$ inch below the costal margin on deep inspiration; there was no change in the urinary findings. The hemoglobin was 90 per cent., the red cells 6,480,000, the white cells 7000, polynuclear neutrophils 79.7 per cent., small lymphocytes 12 per cent., large lymphocytes 5 per cent., eosinophils 2 per cent., basophils 1.3 per cent.

The patient returned August, 1919, almost three years after the original examination, because of a return of the headaches and pain in the right side of the abdomen. One year before, following the extraction of a tooth, she had bled profusely for twenty-four hours. After that her color improved and the headaches disappeared until two months before examination, when they returned, accompanied by marked dizziness. Her face and hands were bluish red, the spleen was palpable 2 inches below the left costal margin, and the liver 1 inch below the right costal

margin. The urine contained a trace of albumin with a few hyaline casts and leukocytes. The combined phenolsulphonephthalein test had dropped to 35 per cent. The blood urea was 24 mg. for each 100 c.c. The hemoglobin was 90 per cent., the red cells 6,620,000, the white cells 8200. Following the withdrawal of 250 c.c. of blood the red cells dropped to 5,040,000, but rose two weeks later to 7,400,000. Again 250 c.c. of blood were withdrawn and the red cells dropped to 6,800,000, and two weeks later to 4,640,000. Following this the patient's general condition improved, her headaches and dizziness disappeared, and her strength returned, but the hot flushes persisted. The spleen diminished in size so that it was just palpable.

Etiology.—The cause of erythremia is unknown. Widal believed that through the loss of splenic function, probably by tuberculosis, the bone-marrow becomes abnormally stimulated, so that hyperplasia and polycythemia result. Osler[17] does not believe that the disease is due to splenic tuberculosis, but to a primary hyperplasia of the erythroblastic bone-marrow. Weber suggests that it may be the result of reversion to or persistence of conditions of fetal and early life in which the bone-marrow is red and still actively engaged in the formation of red cells. Metchnikoff assumed that some toxin of a hemolytic nature is manufactured by the spleen and absorbed in the circulation in minute quantities, not sufficient to cause hemolysis, but sufficient to excite a reaction in the blood-forming organs. Belonovsky has shown that minute doses of a hemolytic serum injected into the blood of anemic persons has raised the number of red cells and the amount of hemoglobin.

Lamson showed that the injection of epinephrin produces an increase in the number of red cells in the peripheral circulation due, he believes, to the fact that the drug causes contraction of the liver capillaries, and many red cells lying dormant in these vessels are thrown into the general circulation. There is also an associated reduction or concentration of the blood-plasma. Lamson concluded that the liver acts as a reservoir for red cells. He also showed that if the injection was made after the ligation of the hepatic artery an increase did not occur.

Following a case of cantharides poisoning with an increase in the number of red cells, Lipsitz, Fuerth, and Cross carried out some experiments on rabbits, and found that cantharides introduced into the stomach of rabbits produces a polycythemia not so transitory as that produced by epinephrin, but lasting in some instances as long as eight days. The authors suggested that in some manner, possibly by hemolysis, cantharides stimulates the blood-forming organs or brings about a concentration of the blood.

Age.—The disease is most commonly seen in the fifth and sixth decades, being comparatively uncommon in early life. Ten of this series of 15 cases occurred between the ages of forty-five and fifty-six. The oldest patient was sixty-two and the youngest twenty.

Sex.—Thirteen of the 15 patients were males, and 2 were females. Other writers reported the proportion of males to females as 2 to 1.

Symptoms.—A persistent and absolute increase in the number of red cells, the bluish-red color of the face and hands, the enlarged spleen, and the abnormalities of the retinal vessels, when associated, are pathognomonic of erythremia.

Christian was the first to call attention to the predominance of nervous symptoms. He emphasized them not because case reports and studies had failed to make mention of their frequent occurrence, but because a failure to keep them in mind very often has led to diagnostic mistakes, and, in some instances, to cerebral operation, with the idea that the symptoms were the result of brain tumor. In Christian's series of 10 patients all but 2 showed very definite nervous symptoms, and in most instances the nervous disturbances were the chief cause of the patient's discomfort. The most frequent symptoms were headache and dizziness.

Eight of our patients gave symptoms referable to the nervous system as their chief complaint, the most common being headaches. Other nervous symptoms complained of were dizziness in 5 cases, auditory disturbances in 2, nervousness in 3, insomnia in 1, disturbances of vision in 2, loss of energy in 3, numbness of

the extremities in 2, loss of memory in 1, and paralysis in 2. In the early stages such symptoms must result from simple circulatory disturbances, and in the later stages from cerebral hemorrhage or thrombosis. Other general symptoms noted were epigastric and left hypochondriac pain, palpitation, anorexia, dyspnea, indigestion, diarrhea, and pain in the back.

Color.—Most writers speak of the color of the skin as cyanosis. Lundsgaard carried out experimental studies on cyanosis, and found that the primary causes of the condition are:

1. Increased carbon dioxid content of venous blood.
2. Decreased oxygen content of venous blood.
3. Increased oxygen unsaturation (reduced hemoglobin) of venous blood. "Oxygen unsaturation" he defines as the difference between the venous oxygen and the total oxygen-combining power of the hemoglobin. In a case of polycythemia he found that:

1. The values for the carbon dioxid were low.
2. The values of the oxygen content in the venous blood were considerably greater than is usually found in normal persons. They were increased in the same degree as the total oxygen-combining power of the blood.
3. The oxygen unsaturation was normal.

As a result Lundsgaard proposes to call the color of the skin in polycythemic patients "erythrosis" in order to distinguish the condition from cyanosis.

In 12 cases of our series mention was made of the color of the skin, and in 11 a distinct erythrosis was present; this is most commonly seen in exposed portions of the body, such as the face and hands. Exposure to cold and mental excitement intensify the color.

The erythrosis often antedates the onset of symptoms by many years, so it is probable that the blood condition exists prior to any definite manifestations. Christian draws this conclusion from observations of high blood counts without symptoms among members of families, other members of which had polycythemia with symptoms. Very little is found in the literature regarding the familial aspect of the disease. Ward reported

a case of erythremia in a young man of twenty-one whose father was suffering from the same disease.

One of our patients mentioned that a brother had a similar reddish complexion, and another stated that her daughter's complexion had always been very red, and had become more marked as she grew older. The father of another patient was known definitely to have erythremia.

It must be borne in mind that a typical erythrosis is not always seen; occasionally pallor is noted. As Osler pointed out in his paper on erythremia or polycythemia with cyanosis,[18] "There may be much variation in the color of people, depending on the condition of the cutaneous vessels and the rate of blood flow. If the capillaries are full and the flow slow, cyanosis predominates, if the current is rapid an arterial color is prominent. In polycythemia usually there is a definite mingling of the two colors, resulting in what might be termed a red cyanosis. What is particularly important from the point of view of diagnosis is that the skin in patients with polycythemia may show pallor due presumably to a vasoconstriction or peripheral circulatory failure, and in these cases the diagnosis is likely to be missed unless a blood count or the finding of an enlarged spleen point the way."

That the color may often change is shown by one of Christian's cases. When his patient was seen after the development of abdominal symptoms, due to mesenteric thrombosis, very little cyanosis was noted, although the patient had shown the typical color during previous examinations.

Hemorrhage.—Bleeding of varying severity is common. It was mentioned in 10 of the case histories; in the other 5 it was not definitely stated that bleeding had not occurred. Hematemesis was noted in 1 case, hematuria in 1, hemoptysis in 2, melena in 3, bleeding gums in 2, epistaxis in 3, menorrhagia in 2, cerebral hemorrhage in 2, and prolonged bleeding after extraction of teeth in 1. As is to be expected, the patient's general condition usually improves following a hemorrhage.

Spleen.—One of the characteristic features of erythremia is the splenomegaly. The spleen is usually only moderately enlarged, rarely comparable to the huge spleen of leukemia. En-

larged spleens varying in size were present in 12 of our cases; they were palpable from the costal margin to the umbilicus.

Eye.—An ophthalmoscopic examination should be made in all cases, as the eye changes, when present, are very typical. An eye examination was made in 13 cases; in 8 definite changes were found; the most common finding was the presence of dark colored dilated tortuous retinal veins. Large dark retinal veins were found in 4 cases, slight venous engorgement with hyperemia of the nerve head in 1 case, small retinal hemorrhages in 1, tortuosity of retinal vessels in 1, increased haze of nasal side of disk in 1, and choked disk in 1. The presence of a choked disk in a case of polycythemia often leads to the mistaken diagnosis of brain tumor.

Urine.—In 9 cases there were urinary changes, and in 5 casts were present. It is interesting to note that 1 case reported by McLester showed a large amount of albumin and many hyaline and granular casts. As the general condition improved under treatment the albumin and casts disappeared.

Lungs.—An *x*-ray of the chest was made in 6 cases, 3 of these showed the presence of an old tuberculosis, and 1 fibrosis.

Blood.—A persistent and absolute increase in the number of red cells is the most characteristic feature of the disease. This increase is variable, having a wide fluctuation in the same person. The highest count observed in our series was 9,120,000 and the lowest 6,160,000. One of our patients gave a history of having had a count of 14,000,000. Counts as high as 15,000,000 have been reported. The hemoglobin in most of the 15 cases was estimated as quite low. In only 5 cases did it reach 100 per cent. or over; the highest was 105; the lowest was 84. This does not coincide with the findings of Lucas; in 111 of his cases all but 4 showed a percentage of 100 or over. The highest reported was 240. The color-index was low. The white count was normal in the majority of the cases; a few patients showed a slight increase, as high as 17,000. There was nothing characteristic in the differential counts. The coagulation time was estimated in 5 cases, all being within normal limits, 1 case six minutes, 2 cases seven minutes, 1 case eight minutes, and 1 case

ten minutes. The bleeding time was taken in 4 cases; in 1 case three minutes, 1 case four minutes, 1 case five minutes, 1 case two and a half hours, but after the administration of calcium lactate it returned to four minutes. The fragility of the red cells was tested in 5 cases. Two showed increased resistance to hypo-isotonic salt solution and 3 were normal. In none of the cases was the total blood volume estimated, but in all the cases reported in which this was done it far exceeded the normal.

Metabolism.—The basal metabolic rate was estimated on one patient. It was +21 per cent.

Pathology.—One patient, a male, aged twenty-one, was operated on for brain tumor, and died following a left temporal decompression. Necropsy revealed marked cyanosis of the face, neck, thorax, and extremities. The sella turcica was enlarged, and the pituitary body about three times the normal size. No tumor of the brain was found. A moderate hydrocephalus was present; the lateral ventricle on the right side contained about three times the normal amount of fluid, and on the left side about twice the normal amount.

The spleen was much enlarged, 25 by 12 by 8 cm., with multiple large infarcts, and marked congestion, and with the scar of an old infarct on the lower border.

The liver was markedly congested.

The kidneys were congested and somewhat enlarged.

The findings in the lungs and heart were negative.

The pituitary body was hyperplastic.

An examination of the bone-marrow was not made.

Gordinier reported a case which came to necropsy. The splenic enlargement was due to swelling of the pulp which was engorged with red cells. The reticulum was not increased and the trabeculæ were not thickened. The bone-marrow was of embryologic type, made up of erythrocytes, normoblasts, and erythroblasts, with various types of leukocytes. No fat was seen. Section of the femur showed a reversion of the normal fatty coloration to the dark pink shade of the embryonic type.

Friedman was able to find the reports of 23 necropsies in the literature. In the majority of the cases no deviation from the

normal histology of the spleen was noted. In 3 cases, however, splenic tuberculosis was found, and in 2 cases vascularity and congestion of the spleen. The most constant findings were a true plethora, since all parts of the body were engorged and the transformation of bone-marrow from the yellow fatty to the livid purple variety with erythroblastic and leukoblastic hyperplasia.

TREATMENT

From the standpoint of a permanent cure very little progress has been made in the treatment of erythremia, but several therapeutic measures produce a temporary reduction in the number of red cells and improvement in the patient's general condition.

The various methods of treatment which have been tried are splenectomy, venesection, application of various rays over the spleen and long bones, and the administration of drugs.

The majority of writers in speaking of splenectomy state that the operation is contraindicated, as removal of the spleen has been rapidly fatal. The operations referred to by numerous authors were performed between 1900 and 1905 by German surgeons and cannot be regarded as conclusive with respect to the effect of splenectomy.

In 3 cases collected by Lucas death resulted in from a few days to six weeks. One of the patients, that of Cominotti, died of sepsis six weeks following the operation; one, Blad's patient, died a few days after the operation from profuse internal hemorrhage; and the third, van de Weyde and van Ijzeren's patient, died twenty-five days after splenectomy; the cause of death was not given. Schneider's patient, who died of tuberculosis seventeen months after the operation, showed at the time of operation (May, 1901) 6,000,000 red cells and 22,000 white cells. One month after splenectomy the red cells had dropped to 4,500,000 and the white cells to 16,000. In December, 1901, the patient developed pneumonia followed by pulmonary tuberculosis. In April, 1902, the red cell count was again above normal. In October, 1902, the red count was 1,385,000 and the white count 55,000, of which 1.4 per cent. were myelocytes, and there were twice as many nucleated red as white cells.

Two, or possibly three, of these deaths might be considered operative.

With the advancement which surgery has made since the time these splenectomies were done, especially with regard to the technic of the operation, the operative mortality should be greatly lessened. Even if the risk of operation can be eliminated, however, the value of splenectomy is, of course, problematic, but it might be considered worthy of trial when other measures have failed, especially in cases with repeated severe hemorrhages from the stomach.

Venesection produces only a temporary diminution in the number of red cells, and even if it is repeated frequently it fails to produce any permanent results. This fact is illustrated by the case reported by Ritchie of an erythremic patient with a large indurated ulcer on the leg which refused to heal. From 300 to 500 c.c. of blood were withdrawn at weekly intervals for six weeks. The ulcer began to improve immediately and completely healed over. Even after the bleedings the red count was the same, 12,000,000, and the hemoglobin rose from 120 to 165 per cent. Venesection does, however, give very definite symptomatic relief and is a procedure to be advocated.

The effect of *x*-ray therapy which has been tried in a majority of the recent cases has been variously reported. In some cases it has been of marked benefit, usually only temporary, however, while in others it has not produced any appreciable change in the number of red cells or the percentage of hemoglobin because of the selective action of the rays on the leukocytes.

Few reports concerning the use of radium have been found in the literature. Sailer tried radium in a case of erythremia after other therapeutic measures had failed. The spleen was greatly reduced in size after four months, the red cells dropped from 7,621,000 to 5,679,000, and the subjective symptoms disappeared. Sailer states that when the treatment is suspended symptoms recur.

The action of radium is similar to that of the *x*-rays; the benefit produced is only transitory. As in the case reported here, a temporary reduction in the number of cells occurred, but even

during the course of the treatment it rose, and the count was the highest that was observed at any time.

Many drugs, such as benzol, the nitrites, the bromids, arsenic, and mercury, have been tried, and, with the exception of benzol, all have been discarded.

The use of benzol as a medicinal agent was suggested by the observations of Selling, who studied its influence in the anemia of factory girls who inhaled benzol gas. His experimental work on animals showed that benzol causes first a marked reduction in the leukocytes and later in the erythrocytes. Severe gastrointestinal symptoms are also apt to follow the treatment, which usually must be administered over a long period of time.

Benzol in some cases has produced very striking results. McLester collected 5 cases, including his own, in which a marked improvement had been obtained by benzol, and another in which it had been unsuccessful. McLester's patient had a red cell count of 7,120,000, a white cell count of 28,000, hemoglobin 85 per cent. Following a five months' administration of benzol with a maximum daily dose of 4 gm. the red cells numbered 6,600,000, the leukocytes 10,000. Within the next weeks the red cells dropped to 5,000,000. The patient had been well only seven weeks when the case was reported. McLester did not consider the patient cured, and believed that another increase would occur requiring further administration of benzol.

Hurwitz and Falconer reported a case treated by the combined use of benzol and *x*-ray, in order to test the value of smaller amounts of benzol when combined with *x*-ray. The patient was given 44 gm. of the drug within a month; it was then stopped, but the *x*-ray treatments were continued about two months. Although considerable reduction in the number of red cells followed the use of benzol alone, they began to approach normal only after the seventh *x*-ray treatment. Hurwitz and Falconer believe that the beneficial effects of the combined treatment may be due to the delayed and cumulative action of the benzol itself, but the other writers failed to reduce the number of red cells with amounts of the drug which they used. Hurwitz and Falconer suggest that *x*-rays may act more destructively on

erythropoietic tissues which have been rendered less resistant beforehand by the toxic action of benzol.

Pickard, in a case in which benzol had failed to give relief, used raw spleen and splenic extract over a period of ten months, with a reduction of the red cells from 10,000,000 to normal and of the hemoglobin from 170 to 100 per cent. The erythrosis and general condition of the patient were greatly improved.

RÉSUMÉ OF SPECIAL TESTS

It may be convenient, as a matter of reference, to group together some of the special examinations made in the cases herewith reported.

Fragility of the Erythrocytes.—Freund and Rexford, from a careful serologic study of a case of polycythemia, found that the red cells in polycythemia are neither more nor less fragile than red cells from normal adults, and that the red cells in polycythemia and the normal red cells are equally resistant to hemolysis. Guinon, Rist, and Simon state that the red cells of their patient resisted hemolysis.

Two of 5 of our cases in which the fragility of the red cells was tested showed increased resistance to hypo-isotonic salt solution and 3 were normal. In another case of erythremia, not included in this series, the fragility was normal.

Coagulation Time.—Although many erythremic patients bleed profusely and for a considerable length of time following cuts and extraction of teeth, the coagulation time (Lee method) in all our cases in which it was estimated was within normal limits, in 1 case six minutes, in 2 seven minutes, in 1 eight minutes, and in 1 ten minutes.

Bleeding Time.—This was estimated in 4 cases, and in 3 it was normal, in 1 case three minutes, in 1 four minutes, and in 1 five minutes. The fourth patient had a bleeding time of two and a half hours (single test, not corroborated), but following the administration of calcium lactate it returned to normal. One patient had a platelet count of 115,000.

Metabolism.—The basal metabolic rate estimated on one

patient was +21 per cent. Maude Abbott in her studies on metabolism found the basal metabolic rate of a polycythemic patient to be +16 per cent. on one occasion and +27.8 per cent. after an interval of five months.

BIBLIOGRAPHY

1. Abott, M. E.: The Determination of Basal Metabolism by the "Respiratory-valve and Spirometer Method" of Indirect Calorimetry, with an Observation on a Case of Polycythemia with Splenomegaly, Can. Med. Jour., viii, 491–509, 1918.
2. Belonovsky, S.: L'influence de l'injèction de diverses doses de sérum hémolitique sur le nombre des elements du sang, St. Petersburg, 1902. Quoted by Lucas.
3. Blad, A.: Abstr. in Fol. Hematol., ii, 185, 1905. Quoted by Lucas.
4. Christian, H. A.: The Nervous Symptoms of Polycythemia Vera, Amer. Jour. Med. Sci., cliv, 547–554, October, 1917.
5. Cominotti, V.: Hyperglobulie und Splenomagalie. Hyperglobulie und Splenektomie, Wien. klin. Wchnschr., xiii, 881–884, September 27, 1900. Quoted by Lucas.
6. Friedman, G. A.: Polycythemia Vera, Med. Rec., lxxxix, 692, 693, April 15, 1916.
7. Freund, H. A., and Rexford, W. K.: Serologic Examination in a Case of Polycythemia, Arch. Int. Med., xvii, 415–419, March, 1916.
8. Gordinier, H. C.: A Case of Polycythæmia Vera with Postmortem Findings, Albany Med. Ann., xxxix, 137–143, April, 1918.
9. Guinon, L., Rist, E., and Simon, L. G.: Splenomégalie chez une cholémique avec cyanose et polyglobulie transitoires, Bull. et mèm. Soc. méd. d. hôp. de Paris. xxi, 786–795, 1904. Quoted by Freund and Rexford.
10. Hurwitz, S. H., and Falconer, E. H.: The Value of Roentgen Rays and Benzene in the Treatment of Polycythemia Vera, Jour. Amer. Med. Assoc., lxx, 1143–1145, 1918.
11. Lamson, P. D., and Keith, N. M.: The Rôle of the Liver in Acute Polycythemia, Jour. Pharmacol. and Exper. Therap., viii, 247–251, May, 1916.
12. Lipsitz, S. T., Fuerth, A. L., and Cross, A. J.: Polycythemia Induced by Tincture of Cantharides, Arch. Int. Med., xx, 913–918, December, 1917.
13. Lucas, W. S.: Erythremia, or Polycythemia, with Chronic Cyanosis and Splenomegaly. Report of 2 Cases with Summary of 179 Cases Reported to Date, Arch. Int. Med., x, 597–667, December, 1912.
14. Lundsgaard, C.: Erythrosis, or False Cyanosis, Jour. Exper. Med., xxx, 295–298, September, 1919.
15. McLester, J. S.: Benzol in the Treatment of Polycythemia Rubra, with Report of a Case, Jour. Amer. Med. Assoc., lxxxii, 1381–1383, May, 1914.

16. Metchnikoff: Quoted by Seufert, E. C.: Erythremia or Polycythemia with Enlarged Spleen and Chronic Cyanosis, Amer. Jour. Med. Sci., cx, 827–835, December, 1910.
17. Osler, W.: Chronic Cyanosis with Polycythæmia and Enlarged Spleen: A New Clinical Entity, Amer. Jour. Med. Sci., cxxvi, 187–201, August, 1903.
18. Osler, W.: A Clinical Lecture on Erythræmia (Polycythæmia with Cyanosis, Maladie de Vaquez). Lancet, i, 143–146, January 18, 1908. Quoted by Christian.
19. Pickard, R. J.: Polycythemia. Preliminary Report of a Case with a Hitherto Increased Resistance of the Red Cells to Hemolytic Amboceptor, Jour. Amer. Med. Assoc., lxvii, 1845–1858, December 16, 1916.
20. Ritchie, H. J.: A Case of Splenomegalic Polycythæmia, Med. Jour. Australia, i, 493, 494, June 15, 1918.
21. Sailer, J.: Polycythemia Treated with Radium, Jour. Amer. Med. Assoc., lxvi, 2032, June 17, 1916.
22. Schneider, N.: (On polyglobulie), Lwow. tygodn. lek., i, 505, 519, 534, 1906. Quoted by Lucas.
23. Selling, L.: A Preliminary Report of Some Cases of Purpura, Hæmorrhagica Due to Benzol Poisoning, Johns Hopkins Hosp. Bull., xxi, 33–37, February, 1910. Quoted by McLester.
24. Vaquez, H.: Sur une forme spéciale de cyanose s'accompagnant d'hyperglobulie excessive et persistante, Bull. méd., vi, 849, 1892. Quoted by Lucas.
25. Ward, G. R.: Some Cases of Polycythæmia, Proc. Royal Soc. of Med., vi, Part ii, Med. Sec., 55–82, February 25, 1913.
26. Weber, F. P.: Critical Review: Polycythæmia, Erythrocytosis, and Erythræmia, Quart. Jour. Med., ii, 85–134, October, 1908.
27. van der Weyde, A. J., and van Ijzeren, W.: Chronische tumor der milt als gevolg van thrombose der v. portal, Nederl. Tijdschr. v. Geneesk., 2. R., xxxix, d. i, 832–838, 1903. Quoted by Lucas.
28. Widal: Quoted by Osler, W., and McCrae, T.: Modern Medicine, 2 ed., Philadelphia, Lea & Febiger, iv, 684–686, 1915.

APLASTIC ANEMIA

A. ARCHIBALD, M. D.

APLASTIC anemia was the name given to a rather rare type of anemia by Ehrlich in 1888, when his attention was called to the condition from observations made on a female patient who developed profound anemia following a severe uterine hemorrhage. Since that time, however, cases similar from a clinical and pathologic standpoint, but differing in etiology, have been reported, in some of which apparent etiologic factors could be demonstrated, for example, acute infections, while in others the cause could not be found. In recent years cases of the latter type have received a fair amount of attention among medical writers. Several theories with regard to the etiology more or less well supported, on a clinical and pathologic basis, have been suggested. The literature was reviewed and brought up to date by Musser in 1914 and by Smith in 1919.

Part of the aim of most writers apparently is to determine whether or not the condition known as aplastic anemia is allied to pernicious anemia. While it is true that an extreme case of aplastic anemia differs very widely both clinically and pathologically from a case of so-called true pernicious anemia, yet there are cases which evidently present characteristics of both. A thorough study of these cases may help greatly in the classification of aplastic anemia. If such cases could be studied from the beginning to the end of the illness, atypical clinical features and atypical blood-pictures might be further explained. . These patients may come for consultation at a time when the clinical picture is atypical of the disease from which they are suffering. I have seen instances in which patients presenting features typical of a secondary anemia later developed pernicious anemia, and again patients with pernicious anemia who developed the clin-

ical picture of aplastic anemia. There is no doubt, therefore, that mistakes in diagnosis may be made and result in much confusion. As is shown by Smith, and also by the case I shall report, absolute dependence cannot be placed on clinical findings in making a diagnosis. In some of the reported cases the clinical findings are relied on for a diagnosis, but such cases should be considered as doubtful, since postmortem findings may not confirm the clinical diagnosis. As I have said, an extreme case of aplastic anemia differs widely, both clinically and pathologically, from the true type of primary pernicious anemia, yet on considering the intermediate cases it would seem that some relation may exist between the two conditions. Some of the reported cases show an extreme aplastic condition of the bone-marrow, with little or no hemolysis, while others show hemolysis as well as a failure to regenerate blood-cells. In pernicious anemia extreme hemolysis is found, accompanied by a hyperplastic condition of the bone-marrow. The following are the principal theories regarding the etiology of aplastic anemia:

1. It is a distinct type of anemia originally due to rapid degeneration of the bone-marrow; hemolysis probably does not take place, the bone-marrow degeneration being due to the onslaught of some unknown toxin.

2. It is a type of pernicious anemia; there is some hemolysis, but the toxin attacks the bone-marrow as well as the red blood-cells.

3. There may be some hereditary weakness of the bone-marrow and it falls an easy prey to the action of a toxin.

Unfortunately, my case was not completely studied from a clinical-research point of view. These patients, as a rule, are extremely ill, and examinations necessary to complete definite clinical data would be detrimental to their satisfactory progress. Other difficulties arise in individual cases, making it impossible to get all desirable data, including postmortem examination.

REPORT OF A CASE

CASE A288809, a Danish farmer, aged fifty-seven, came for examination September 11, 1919. The patient's family history

is unimportant. He had pneumonia eleven years before; he was weak, pallid, dyspneic, and had a poor appetite. He stated that his health had been excellent until three and a half months before, when he developed dyspnea and weakness, which gradually became more marked. Five weeks prior to examination he had toothache, and several teeth which the dentist said were ulcerated were extracted; since that time his mouth had been sore, but his tongue was not sore, as is common with pernicious anemia. Pallor was first noticed from four to six weeks before and had gradually increased in severity. There was no bleeding from the teeth or elsewhere; no numbness or paresthesia and no gastro-intestinal symptoms, except loss of appetite. All symptoms evidently had progressed rapidly in the past six weeks, and the patient lost 20 pounds in weight.

Objectively, the patient was described as a well-nourished man having a lemon-yellow appearance and pale mucous membrane. His teeth were in poor condition, with a fairly marked degree of pyorrhea. The tongue looked clean and appeared normal. Nothing of importance was found in examination of the chest and the abdominal examination was entirely negative. The Wassermann test, the Widal test, and blood-cultures were all negative. The urinalysis was negative until the day of death, when a trace of albumin and a few hyaline casts were found. The hemoglobin was 30 per cent., erythrocytes 1,590,000, leukocytes 1800, color index 0.9+; the differential count showed polymorphonuclear neutrophils 11 per cent., small lymphocytes 85 per cent., large lymphocytes 3 per cent., eosinophils 1 per cent. Two hundred cells were counted and 46 normoblasts were seen. There were moderate anisocytosis, slight poikilocytosis, and slight polychromatophilia. The patient had in his possession the report of a blood examination made four days before his admission to the clinic which showed hemoglobin from 40 to 50 per cent.; erythrocytes 3,200,000, leukocytes 5200, polymorphonuclears 12.5 per cent., small lymphocytes 72.5 per cent., large lymphocytes 22 per cent., eosinophils 0.5 per cent., transitionals 1.5 per cent., slight poikilocytosis; normoblasts were seen, but the number was not stated. The patient was under

our observation until his death, eleven days later. During that time the temperature ranged from 99.2° to 104° F. except on one occasion, when it registered 98.4° F. Treatment consisted mainly in the administration of a liberal soft and fluid diet, Blaud's tablets and Fowler's solution were given. The patient was not transfused, but he was given salt solution by hypodermoclysis. September 15th the hemoglobin was 26 per cent., the erythrocytes were 1,330,000, and the leukocytes 1800. September 22d the hemoglobin was 23 per cent.; unfortunately, a complete blood count was made only once. The patient gradually lost strength, became more pale, and finally died September 27th.

A few days after the patient was first seen he developed a subacute ischiorectal abscess which I believe had no influence on the clinical course of the disease. It is to be regretted that the usual tests supposed to determine the presence of hemolysis were not made. Schneider states that in so-called aplastic anemia the duodenal pigment values are subnormal.

PATHOLOGIC EXAMINATION

The findings were practically as follows: Primary acute aplastic (?) anemia; almost complete fatty replacement of the marrow of the long bones; slight hyperplasia (?) of the marrow of the sternum and ribs; marked pallor of the skin of the body generally and of all parenchymatous organs; unusually thin, watery blood; decreased amount of blood in the heart and the great vessels; petechial hemorrhages in the skin of the shoulder girdle, in the peritoneum, the pleura, and in the mucous lining of the greater antrum of the stomach; extensive fatty changes in the myocardium and, to a lesser degree, in the liver; marked pyorrhea alveolaris; slight chronic diffuse nephritis—finely granular red kidneys; rather large ischiorectal abscess; marked edema of the scrotum and prepuce; moderate bilateral hypostatic pulmonary hyperemia; quite marked nodular fatty fibrous and calcereous changes in the lining of the aorta and its main branches; marked nodular hypertrophy of the prostate gland; slight right diaphragmatic fibrous pleuritis; slight fibrous ad-

hesive perisplenitis; hypodermoclysis puncture needle wounds of both breasts; salt solution (?) edema of the tissues of both breasts.

The most strikingly noteworthy abnormality of the outside of this body was the extreme pallor of the skin—a pallor which, in artificial light, presented a yellowish tint. The mucous membranes of the mouth and conjunctivæ were almost colorless. In the skin of the shoulder-girdle and over the scapulæ behind were many bright red or slightly faded violet tinted hemorrhages; these varied in size from that of the point of a pin to 3 mm. in diameter. Their bright color indicated that they were recent; none were found on the arms, as is so often the case in the petechiæ of endocarditis. The gums were shrunken from the roots of the teeth, which were decayed. The tonsils were not enlarged to the feel. The subcutaneous fat through the thickest part of the abdominal wall measured from 2 to 3 cm. The peritoneum, unusually pale and faded appearing, was possibly a little more moist than normal from an increase in clear, straw-colored fluid. The luster of the peritoneum was present throughout. The bowel contained only a very little soft material. Here and there throughout the peritoneal covering of the small bowel and the mesentery were scattered petechiæ similar to those seen in the skin of the shoulder-girdle. Similar petechiæ were found in the visceral pleura. As the chambers of the heart and the great vessels were opened the blood was found to be greatly decreased in amount and thin and watery.

The parenchymatous tissues of the body generally presented the pale appearance of profound anemia. In fact, the anemia was one of the most striking gross abnormalities noted. In the heart muscles there was unmistakable evidence of very extensive fatty changes, a feathery, so-called thrush-breast appearance of the myocardium as seen through the endocardium. Similarly there were mottled areas of yellow fatty material in the liver.

Possibly the most noteworthy gross abnormalities in the body were found in the bone-marrow. The marrow of the right tibia was a lemon yellow, absolutely devoid of a tint of blood.

This is most striking in contrast to the marrow of the tibia in primary progressive pernicious anemia. The marrow of the sternum and ribs, on the other hand, presented the normal faded pink appearance; in fact, it was a little more red than normal. The marrow activity seemed to be limited to some of the flat bones.

HISTOLOGIC EXAMINATION

The heart and liver showed marked fatty changes, the adrenal, moderate fatty changes; the lung was hyperemic; the kidney showed a slight diffuse nephritis; the spleen had an increase of red cells in the pulp; in the bone-marrow from the tibia were a few small areas showing immature cells of the myeloblastic and myelocytic types, particularly the former; only an occasional nucleated red cell was found; all of these were normoblasts. There were a few mitotic figures, and only small areas of myeloblastic tissue. The bone-marrow of the rib showed increased activity, many nucleated red cells; both normoblasts and megaloblasts were present, and numerous mitoses were seen. There were numerous myeloblasts and myelocytes. The most noteworthy feature was the presence of megaloblasts.

The more important symptoms supposed to be typical of so-called aplastic anemia and those of primary pernicious anemia have been tabulated side by side as follows:

Clinical Findings

Aplastic Anemia	*Pernicious Anemia*
Onset—usually early in life.	Onset in adult life.
The cause—usually unknown.	Cause—unknown.
Onset and progress acute and rapid.	Onset and progress slow and chronic.
No remissions.	Remissions.
Hemorrhages and petechiæ—common.	Hemorrhages and petechiæ somewhat rare.
Fever—usually.	Fever—none or slight.
Weakness, dyspnea, etc.	Weakness, dyspnea, etc.
Mouth not sore.	Mouth sore.
No numbness.	Numbness.

Blood-picture	
Low color index.	High color index.
Leukopenia.	Leukopenia, especially in advanced cases.
Relative increase in small lymphocytes.	Relative increase in small lymphocytes.
No evidence of regeneration, for example, in the presence of normoblasts and megaloblasts.	Evidence of regeneration.
No evidence of hemolysis, for example, the presence of a yellow tint and urobilinogen in the urine and in the duodenal contents.	Evidence of hemolysis.
Pathologic Findings	
Aplastic bone-marrow.	Hyperplastic bone-marrow.
Usually no evidence of hemolysis.	Evidence of hemolysis.

From this tabulation it will be seen that the symptoms and clinical findings conform, for the most part, to those under the heading of aplastic anemia, but at the same time some features typical of pernicious anemia are present. The onset of the illness was sudden and progressively rapid, with no remissions. There was no numbness of the extremities or sore tongue, as is often seen with pernicious anemia. There was, however, marked pyorrhea. There were no hemorrhages, but subcutaneous petechiæ were present. There was fever every day except one, reaching as high as 104° F. It is evident that a definite diagnosis could not be made from the blood findings alone; they conformed in part to those which are supposed to be typical of aplastic anemia, and at the same time had features of the blood-picture of pernicious anemia. The color index is not low, yet not above 1, as is usually the case in pernicious anemia. The marked leukopenia with a relative high percentage of small lymphocytes is typical of aplastic anemia, and is not usually found in pernicious anemia except in advanced cases. The finding of 46 normoblasts, moderate anisocytosis, slight poikilocytosis, and slight polychromatophilia is strongly suggestive of pernicious anemia. These findings may be accounted for by the fact that the rib bone-marrow showed slight hyperplasia. Had the blood been examined early in the disease, more marked evidence of

blood regeneration might have been found. It is seen, therefore, that the color index of 0.9 and the marked leukopenia with a relatively high percentage of small lymphocytes are in favor of aplastic anemia, but the evidence of blood regeneration proves there is still some hyperplastic bone-marrow, as is seen in cases of pernicious anemia. With regard to hemolysis, the only evidence which I can suggest is the lemon-tinted appearance of the patient, as is seen in cases of pernicious anemia. In aplastic anemia the complexion is usually described as ashen gray, and this is thought to be due to the fact that hemolysis does not take place. Regarding the nervous system, it is noteworthy that there were no symptoms and no objective findings indicating pathologic changes in the cord.

From these data it will be seen that the case under discussion presents a type of anemia which might be considered intermediate between aplastic anemia and pernicious anemia. Pathologic conditions were found that are typical neither of so-called aplastic anemia nor of pernicious anemia. If the long bones alone had been examined, it might have been taken for granted that aplasia of all the bone-marrow existed, and in this respect some of the reported cases of aplastic anemia should be considered as doubtful. The other pathologic findings are typical of those found in severe anemias and indicate the influence of some powerful toxin.

I have no definite proof on which to form an opinion whether aplastic anemia is or is not allied to pernicious anemia, but it should not be forgotten that cases do occur which have characteristics of both diseases, not only clinically but pathologically.

BIBLIOGRAPHY

1. Ehrlich, P.: Ueber einen Fall von Anämie mit Bemerkungen über regenerative Veränderungen des Knochenmarkes, Charité Ann., xiii, 800, 1888. Quoted by Musser.
2. Musser, J. H., Jr.: Study of a Case of Aplastic Anemia, Arch. Int. Med., xiv, 275–288, August, 1914.
3. Schneider, J. P.: Aplastic Anemia, Amer. Jour. Med. Sci., clvi, 799–807, December, 1918.
4. Smith, L. W.: Report on an Unusual Case of Aplastic Anemia, Amer. Jour. Dis. of Children, xvii, 174–194, March, 1919.

TUBERCULOSIS OF THE SPLEEN

H. Z. GIFFIN, M. D.

So-called primary tuberculosis of the spleen is not exceedingly rare. It is not possible to say that tuberculosis of the spleen is ever strictly primary, for it is almost certain that in every case an original focus was formerly present elsewhere in the body, although no evidence of tuberculosis may be found at the time of examination. Patients in whom the original focus has healed or in whom other foci are of definitely secondary importance may be said to have primary tuberculosis of the spleen. The clinical characteristics of such cases are of considerable interest.

The history and the findings in a case of primary tuberculosis of the spleen which I wish to present would seem to indicate that this disease may produce an anemia of the hemolytic type, and that splenectomy may result in complete cure.

Case 152671.—H. L., a girl aged sixteen, gave a four-year history of pallor, indefinite jaundice, and epistaxis. The patient had had pneumonia three years before, and after that time increasing pallor, weakness, dyspnea, and pain in the splenic region. She had not been robust since scarlet fever at the age of four. Her condition had become gradually worse for several months preceding examination. Enlargement of the spleen had previously been definitely noted, and probably dated from the onset of pain in the region of the spleen three years before. The blood count was as follows: Hemoglobin 50 per cent., erythrocytes 2,940,000, color index 0.8+, leukocytes 6800, polynuclear neutrophils 71.7 per cent., small lymphocytes 18.7 per cent., large lympocytes 7.3 per cent., eosinophils 2.3 per cent.,

basophils 0, normoblasts 1, anisocytosis moderate; poikilocytosis slight; polychromatophilia slight; coagulation time five minutes.

Notwithstanding a color index of less than 1, the occurrence of normoblasts in the blood-stream, together with considerable deformity of the erythrocytes and the clinical appearance of hemolytic activity suggested by the icterus, led to a diagnosis of atypical pernicious anemia. This diagnosis was corroborated by the findings of 1000 spectroscopic units of urobilinogen and 5000 units of urobilin in the duodenal contents (modified Schneider method). The Wassermann test was negative. A diagnosis of hemolytic jaundice seemed to be excluded by the absence of increased fragility of the red cells and a history which was negative for recurrent jaundice and crises. However, the spleen was unusually large for pernicious anemia. There had been no definite former history of tuberculous peritonitis and there was no evidence of tuberculosis elsewhere in the body. Splenectomy was performed March 15, 1916. The spleen weighed 508 gm. Tuberculous splenitis and perisplenitis were present. The spleen was completely adherent and a localized tuberculosis of the omentum and peritoneum was disclosed. The pelvic organs seemed to be normal.

The patient was examined again July 27, 1918, more than two years after operation, at which time she weighed 133 pounds and showed no evidence of anemia. The erythrocytes were 4,800,000 and a differential count was not abnormal. A letter of June, 1919, three years and three months following operation, indicates that her good general condition has been maintained. A complete and what would seem most likely to prove to be a permanent cure has evidently occurred.

The most interesting features of this case are the marked anemia with relatively low erythrocyte count, the presence of an occasional normoblast in the blood-smears, together with a deformity of the erythrocytes and the clinical and laboratory findings of increased hemolysis evidenced by the icteroid tint of the patient and the very marked quantitative increase of abnormal bile pigments in the duodenal contents. The post-operative course was different from the course following the re-

moval of the spleen for pernicious anemia, and the features of the case were in no way typical of hemolytic jaundice, so that it would seem most likely true that the condition of the patient was secondary to a localized splenic and perisplenic tuberculosis. It would follow, then, that it may be possible for tuberculosis of the spleen to produce an anemia of the hemolytic type analogous in many respects to the anemia of pernicious anemia and hemolytic jaundice.

Quénu and Baudet in 1898 fully described so-called primary tuberculosis of the spleen and emphasized the possibility of curing the condition by means of splenectomy.

Winternitz in 1912 carefully collected all cases of so-called primary tuberculosis of the spleen which he was able to find in the literature, and published a tabulation of the important details in connection with these cases. His total is 51; 34 of these cases were diagnosed at necropsy and 17 at operation. Of the 17 patients operated on, 16 were splenectomized, and 10 recovered. It is Winternitz's opinion that death invariably occurs if the spleen is not removed in these cases; 11 of 26 patients in whom examination of the blood was made, showed a moderate degree of anemia. Extreme anemia was not present in any case. On the other hand, 6 patients of this series showed polycythemia.

Lewis and Margot in 1914 and 1915 reported in three papers the results of their experimental work on the effect of splenectomy in albino mice on the resistance to tuberculous infection. They found that the removal of the spleen greatly increases the resistance of the animal to tuberculosis, and they concluded that this increased resistance following splenectomy in mice is probably due to the loss to the organism of a function of the spleen. This function seemed to be partially restored by the feeding of fresh splenic tissue. It is conceivable, then, if this work is corroborated and holds true for other animals, that removal of the spleen in patients with tuberculosis may increase the resistance of the individual to tuberculous infection, at any rate, tuberculous infection of the bovine type.

It may be concluded that splenectomy is indicated in cases of more or less definitely localized tuberculosis of the spleen. A

sufficient number of recoveries have been recorded in the literature to lead to this conclusion. The case herewith reviewed also corroborates this statement.

Secondary tuberculosis of the spleen is quite common. The involvement of the spleen is usually miliary in type and very rarely caseous. Statistics of postmortem examinations in cases of tuberculosis in childhood show involvement of the spleen in from 50 to 66 per cent. In adults with tuberculosis the spleen is involved in approximately 20 per cent. of the cases. The involvement of the spleen with respect to the abdominal organs has been regarded as somewhat analogous to the lungs with respect to the thorax. Affection of the lymphatic glands is doubtless the most common form of abdominal tuberculosis, and involvement of the spleen is second in frequency.

It is especially interesting to observe the atypical types of disease which have been associated with tuberculosis of the spleen. The association of polycythemia with tuberculosis of the spleen has been fully considered in the literature. A satisfactory study of blood counts and of the degree of hemolysis has not, however, been made. In none of the cases reviewed in the literature has the anemia been of extreme grade.

The erythrocytes have never been reported below 3,500,000. In the first case presented the anemia was of extreme grade and simulated in many respects pernicious anemia. A second patient has come under observation in whom the clinical characteristics simulate hemolytic jaundice.

CASE 190774.—W. W. V., a woman aged thirty-two, gave a clinical history which was in some respects suggestive of hemolytic jaundice, with the onset of symptoms at the age of twenty-five. At twenty-eight years of age an attack of abdominal disease occurred with the features of tuberculous peritonitis. Splenic enlargement dated from that time, and, on examination at the age of thirty-two, extended almost to the level of the navel. A moderately severe anemia with a hemoglobin of 56 per cent., and an erythrocyte count of 3,680,000, giving a color index of 0.7+ were present. The leukocyte count was 16,400,

while a differential count showed nothing definitely abnormal aside from the presence of an occasional myelocyte. An examination of the erythrocytes revealed increased fragility to hypo-isotonic salt solution, which is quite constantly present in cases of hemolytic jaundice. In view of a history which was suggestive of tuberculous peritonitis and in the light of former experience, however, it was suggested that a localized tuberculous splenitis might be present. Moreover, *x*-ray examination of the chest revealed a healed lesion in the upper lobe of the right lung. Splenectomy was performed April 25, 1917. The spleen was completely enveloped in adhesions, it weighed 625 gm., and microscopic examination showed definite evidence of tuberculosis. In this case, then, the condition simulated, but was not entirely typical of, hemolytic jaundice. The patient returned for examination two years and four months after splenectomy and was found to be in excellent health.

A case of tuberculosis has recently come to necropsy in which the clinical characteristics were those of an acute anemia of the primary type.

CASE 276901.—C. L. R., a man aged forty-five, gave a three-year history of increasing weakness and numbness of the extremities, together with an intermittent history of sore mouth and tongue. Pallor seemed to have developed more recently. More or less gastric distress had been present, but the history was not suggestive of tuberculous peritonitis. During the month preceding examination at the clinic the patient's health had rapidly deteriorated with loss of weight, bleeding from the gums, and anemia. Examination of the blood revealed a hemoglobin of 48 per cent. and an erythrocyte count of 2,880,000, with color index of 0.8+. The erythrocyte count fell steadily after that time and before death was 1,530,000. The color index was constantly in the neighborhood of 0.9+ or 1.0. A marked leukopenia was present, the leukocyte count dropping to 1000, of which approximately only 25 per cent. were polynuclear neutrophils. Normoblasts were present and there was marked deformity of the erythrocytes. The blood-picture was suggestive

of an acute aplastic anemia, or the terminal stage of pernicious anemia. *x*-Ray examination of the chest was negative for tuberculosis. The presence of considerable fever led to the suspicion of a septicemia, but blood-cultures were negative; it also was suggestive of the existence of an acute miliary tuberculosis.

A steady decline occurred and the patient died eleven days after admission and approximately six weeks after the acute exacerbation of his condition. Necropsy revealed the presence of an aplastic anemia. The marrow of the long bones was entirely replaced by fat. Miliary tuberculosis of the spleen was present together with a tuberculosis of the tracheobronchial lymph-nodes. An acute generalized miliary tuberculosis, however, was not present, and the lesions in the spleen and in the lymph-nodes were not of an acute character.

It is true that in this case the association of tuberculosis of the spleen with a clinical picture and pathologic findings closely simulating acute aplastic anemia may have been coincidental.

A further instance of an unusual association of diseases and the production of atypical manifestations is seen in the following case in which the clinical characteristics were those of cardiac decompensation and polyserositis and the blood count that of a chronic form of myelogenous leukemia.

CASE 274167.—C. M., a man aged thirty-seven, gave a history of splenic enlargement and pain in the region of the spleen for six months preceding his examination in June, 1919. Gradually increasing weakness, shortness of breath, and loss of weight had occurred following an acute cold six weeks before admission. Physical examination disclosed evidence of cardiac insufficiency, pericarditis with effusion, a moderate nephritis, a splenic enlargement extending to the midline and to the left iliac spine, and ascites. Fever, usually between 100° and 101° F. was present. The examination of the blood showed a moderately severe secondary anemia and the leukocyte counts varied from 19,900 to 58,500, with 17 per cent. of myelocytes present in smears. The patient died one month later, July 14, 1919. Necropsy revealed a very large spleen, measuring 25 by 16 by

9 cm. Microscopic study of the involved organs led to a diagnosis of miliary tuberculosis, possibly of the bovine type.

The clinical findings in this case were those of a myelogenous leukemia with somewhat atypical features. The extreme splenic enlargement was in keeping with these findings, and it is likely in this instance that the tuberculosis was a secondary infection and that it modified the course of the disease in a case of previously unrecognized myelogenous leukemia.

CONCLUSIONS

Our experience with so-called primary tuberculosis of the spleen leads to the following deductions:

1. Splenectomy is indicated in cases of more or less definitely localized tuberculosis of the spleen.

2. From the standpoint of diagnosis, tuberculous splenitis should be considered in every case with marked splenomegaly in which the findings are not clearly those of some other disease. Primary tuberculosis of the spleen may simulate pernicious anemia. The coincidental association of tuberculosis with diseases of the spleen and blood will explain a certain small percentage of atypical cases.

BIBLIOGRAPHY

1. Lewis, P. A., and Margot, A. G.: The Function of the Spleen in the Experimental Infection of Albino Mice with Bacillus Tuberculosis, Jour. Exper. Med., xix, 187–194, February, 1914.
2. Lewis, P. A., and Margot, A. G.: The Function of the Spleen in the Experimental Infection of Albino Mice with Bacillus Tuberculosis. Second paper, Jour. Exper. Med., xxi, 84–90, January, 1915.
3. Lewis, P. A., and Margot, A. G.: The Function of the Spleen in the Experimental Infection of Albino Mice with Bacillus Tuberculosis. Third paper, Jour. Exper. Med., xxii, 359–365, September, 1915.
4. Quénu, E., and Baudet, R.: La tuberculose primitive de la rate, Rev. de gynéc. et de chir. abd. ii., 317–352, 1898.
5. Winternitz, M. C.: Tuberculosis of the Spleen, Arch. Int. Med., ix, 680–697, June, 1912.

TWO PATIENTS WITH PERNICIOUS ANEMIA ALIVE MORE THAN THREE YEARS AFTER SPLENECTOMY

T. L. SZLAPKA, M. D.

ALTHOUGH splenectomy for pernicious anemia has been a disappointment and the operation has now been largely abandoned, it will be of interest to discuss the result in 2 of our cases. A total of 50 patients whose condition was definitely diagnosed as pernicious anemia were operated on in the Mayo Clinic between January 1, 1910 and April 1, 1917; 42 of these patients are now dead; 3 deaths were operative. All of the 8 surviving patients have been splenectomized about three years and six months. Two of these 8 patients have been chosen for presentation, not in order to furnish any conclusions, but because of their interesting features.

CASE I (A151088).—M. R., an unmarried woman, aged twenty-nine, presented herself for examination January 31, 1916. The patient's family history was unimportant. Her menses were normal except for a slight scantiness of the flow. She had had repeated attacks of tonsillitis, smallpox, and a "sore mouth" off and on for several years. Her present illness began about one year before with indefinite soreness in the back, followed by boils, which persisted for about two months, after which she began to feel weak. Her relatives noticed pallor of skin and some yellowness of eyes. The weakness became more and more marked, and later was accompanied by dyspnea. The patient complained of a little numbness and tingling of the extremities. Except for a slight short improvement for a month or two her condition became progressively worse. Another boil had been noticed just before her examination here.

On physical examination we noted the marked pallor. The spleen was easily felt with the patient lying on her right side. The liver was not palpable. Both legs were slightly edematous with scars of the recent boils. The right knee-jerk was diminished, the left was about normal. A soft systolic murmur could be heard over the base of the heart. The systolic blood-pressure was 132, the diastolic was 82, the pulse was 104, and the temperature 99.6° F. No record was made of the condition of the teeth and tonsils.

A twenty-four-hour specimen of urine was negative except for a trace of albumin. The blood Wassermann was negative. January 3d the hemoglobin was 28 per cent., erythrocytes 1,530,000, leukocytes 4100, polynuclear neutrophils 53 per cent., small lymphocytes 33 per cent., large lymphocytes, 6.7 per cent., eosinophils 2.7 per cent., neutrophilic myelocytes 4.7 per cent., normoblasts 17, megaloblasts 1, marked anisocytosis and poikilocytosis. The resistance of the red blood-cells to hypotonic salt solution was normal. Large doses of iron and Fowler's solution were prescribed and one transfusion by the citrate method was done. February 9th, the day after the transfusion, examination of the blood showed the hemoglobin to be 35 per cent., erythrocytes 1,580,000, leukocytes 4600, with a negative differential count in the course of which 18 normoblasts and 2 megaloblasts were seen. Five days later, February 14th, a splenectomy was performed (Balfour). The spleen was about four times its normal size, weighing 530 gm., but showed only a chronic splenitis. The abdominal exploration was otherwise negative. The liver was not enlarged.

March 3d, three weeks after the splenectomy, the hemoglobin was 30 per cent., erythrocytes 1,360,000, leukocytes 10,000, polynuclear neutrophils 60 per cent., small lymphocytes 34 per cent., large lymphocytes 2 per cent., eosinophils 3 per cent., normoblasts 556, megaloblasts 19. The icterus had become less marked, but the general improvement was only slight, much less noticeable than that seen in most of our other cases. Deep bone pains in both legs, spine, and ribs lasted two weeks, and the sternum was tender on pressure. About

six weeks after operation the patient developed a cold with pain below the left breast lasting three days, with fever up to 100° F. Improvement then became more marked; the appetite was very good. The icteroid tinge was slight, only just noticeable, but the skin was a little dusky. April 17th the hemoglobin was 47 per cent., erythrocytes 2,160,000, leukocytes 10,000, polymorphonuclears 60.3 per cent., the differential count being otherwise unimportant. Urobilinogen and urobilin were present in the urine. The duodenal contents examined for bile pigments after the method of Schneider showed: bilirubin +++, urobilinogen 6600 units, urobilin 8600 units, total 15,200 units. Iron and arsenic medication was continued.

Two months later, on re-examination, the patient looked quite well, the complexion seemed to be clearing up, yet she stated that she was gradually getting weaker. Her mouth was slightly sore. Her extremities were not numb. The hemoglobin was 41 per cent., the erythrocytes 1,980,000, color index 1+, and leukocytes 7000. Slight increase was noted in the resistance of the erythrocytes to hypotonic salt solution. The duodenal contents showed some improvement: bilirubin ++, urobilinogen 2400 units, urobilin 600, total 3000.

August 1st, after another interval of two months, the patient again presented herself for observation. She had been growing steadily weaker, had lost her appetite, and the yellow color was more marked. She had no bone pains, but some sore mouth. August 3d, six months after splenectomy, the hemoglobin was 35 per cent., erythrocytes 1,960,000, leukocytes 10,800; in making the differential count there were counted 55.7 per cent. polynuclear neutrophils, 1.7 per cent. neutrophilic myelocytes, 372 normoblasts, and 10 megaloblasts. The patient was given one transfusion, and August 11th the hemoglobin was 38 per cent., the erythrocytes 2,000,000, leukocytes 11,800, of which 73 per cent. were polynuclear neutrophils; normoblasts 330, megaloblasts 11. The duodenal contents on the day before transfusion showed bilirubin +++, urobilinogen 1000 units, urobilin 600 units, total 1600 units, a further lowering which was considered favorable.

September 27th, again after two months, the patient reported for examination, stating that for some time she had improved somewhat following her last examination, but had begun to go down again. Her color was poor and yellowish; there was no numbness of the extremities or sore mouth. Her condition was aggravated by a slight cold. The hemoglobin was 35 per cent., erythrocytes 1,540,000, leukocytes 14,600, polymorphonuclear neutrophils 50 per cent. A transfusion was given. Four days later the patient developed a fever of 105° F., with diarrhea and abdominal cramps and vomiting, lasting two days, which may have been the result of the transfusion. She still failed to improve. Her liver was found to have become considerably enlarged and, at Dr. Giffin's suggestion, the application of radium was tried; 120 mg. hours were given, followed by another blood transfusion about a week after the preceding one. October 10th the hemoglobin was 30 per cent., erythrocytes 1,260,000, leukocytes 11,200, of which 57 per cent. were polynuclear neutrophils, normoblasts 166.

In December, eight months after operation, the patient again reported, stating that she had continued to gain after the transfusions and the radium treatment. Her appetite was good. The yellowness had gradually disappeared and her color was good, especially during the preceding month. She was gaining in weight, but still was unable to do much. Her legs pained and ached. Iron and arsenic were continued. The hemoglobin was 65 per cent., erythrocytes 2,960,000, normoblasts 10. December 4th the duodenal contents showed urobilinogen 600 units, urobilin 600 units, total 1200 units. The liver was normal in size.

During the following two months, January and February, 1917, the patient improved rapidly, and from then on she described herself as being in perfect health. The same opinion has since been expressed by her physician from time to time. Unfortunately, we have not had the opportunity of re-examining her. The blood examinations made by her family physician have given readings of hemoglobin between 80 and 98 per cent.,

erythrocytes between 4,500,000 and 5,000,000; no differential counts have been available.

February, 1919, the patient was married. She continues to be apparently entirely well except for a little sore mouth and some pains in the right hypochondrium. In her last report, June 23, 1919, she stated that she had been doing all her own housework and had never felt so well in her life.

It is now about four and one-half years since the onset of this patient's symptoms. The case is interesting because she has survived her operation for three years and seven months, during which time frequent clinical observations could be made. Her condition is now excellent and has been so continuously for at least the past one and one-half years. However, the rather stormy early postoperative course is worthy of study:

1. The numerous attacks of tonsillitis and the furunculosis which preceded her illness, to say nothing of the possibility of dental infection, may be considered as possible factors in the production of the disease.

2. Although the spleen was much enlarged, only a "chronic splenitis" was found on microscopic examination.

3. At operation the liver was not enlarged, but later it increased considerably in size, the enlargement being accompanied by a deterioration of the patient's general condition. The possibility that the large liver also was actively destroying blood led us to try radium, largely as an experiment, the patient's critical condition at the time making this justifiable. A transfusion just before and just after the radium exposures may have been factors in producing the marked subsequent improvement. Previous transfusions, however, were apparently without effect.

4. The bile pigments in the duodenal contents were considered to be a fairly satisfactory index of hemolytic activity. The values as estimated by a modified Schneider technic in other patients who have been splenectomized have promptly diminished after splenectomy. In this case, however, they were extremely high immediately after operation, and their fall was very gradual, suggesting that the operation had removed only a fraction of

the hemolytic factor. The patient's condition improved coincidently with the decrease of hemolysis, as indicated by the fall in duodenal values to 1200 units, a figure still somewhat in excess of normal. The decrease in urobilinogen from 6600 to 600 units, in the light of our other cases, seems important.

5. The bone pains and tender sternum may well be interpreted as indicative of an active marrow.

6. The blood findings ran parallel with the patient's general improvement. A shower of normoblasts into the circulating blood in pernicious anemia immediately after splenectomy is quite the rule, and may be interpreted as the active response of the bone-marrow after the removal of the overload of blood destruction. The persistent presence of normoblasts here suggests a bone-marrow which has suffered only slight damage and is making strong efforts to maintain the lead in the race between blood production and blood destruction. The tendency of the differential leukocyte count to retain a predominance of polymorphonuclears was also considered as favorable.

7. Further favorable observations are the freedom from diarrhea, the almost complete absence of central nervous involvement, and the slight complaint of "sore mouth."

8. The advisability of removing all foci of infection should be considered in this case. As a rule, such procedures do not affect the essential factors of the disease, however, and may at times be temporarily harmful. It may well be that any infection which might have been a factor in the production of this type of anemia ultimately becomes quiescent and unimportant after having achieved a permanent damage to the organism.

CASE II (A153395).—Mrs. H., aged forty-three, was first examined in this clinic February 28, 1916. The patient is a native of Minnesota. She had been married twelve years and had had 5 children. The family and menstrual histories were negative. She had had scarlet fever at twelve, and smallpox at twenty-eight. Her present illness began about a year before coming for examination, with weakness, shortness of breath, and

exhaustion on slight exertion. The hemoglobin had been 40 per cent. about three months before and had improved somewhat on iron and arsenic. Six weeks before, after a chill, the patient had again become rapidly worse and had been confined to bed. Enlargement of the spleen had first been noted a month before. Her appetite was good, the bowels slightly costive. She had had sore mouth recently, but no paresthesias of the extremities. Pallor was increasing and slight icterus had developed. February 29, 1916, the hemoglobin was 28 per cent., erythrocytes 1,200,000, leukocytes 2300, polynuclear neutrophils 68.3 per cent., small lymphocytes 27.3 per cent., large lymphocytes 2.7 per cent., eosinophils 0.3 per cent., neutrophilic myelocytes 1.3 per cent., normoblasts 6, megaloblasts 1, with marked anisocytosis and poikilocytosis. There was no increase in the fragility of the red blood-cells. The spleen was easily felt about 2 to 3 inches below the ribs and the hepatic dulness was slightly increased. The Wassermann test was negative. Urobilin was present in the urine, but urobilinogen was absent. Routine urinalysis showed a trace of albumin. Examination of the duodenal contents, by the modified Schneider technic,[1] showed bilirubin +++, urobilinogen a trace, urobilin 3500 units. The examination of the tonsils was not recorded. All the teeth had been extracted at least ten years before. A transfusion was done March 1st, following which the blood gradually improved to 59 per cent. hemoglobin and 2,530,000 erythrocytes. March 29th a splenectomy was performed (W. J. Mayo). The spleen was found to be "about two and one-half times its normal size; the liver was large and somewhat dark in color, but free from disease, as were also the ducts and the pancreas. The uterus was atrophic and contained a small fibroid of no consequence." The spleen weighed 450 gm. and showed a "chronic splenitis." The patient gradually gained strength after the operation. The icteroid tinge disappeared. April 22d the duodenal contents were light yellow, with only 200 units of urobilin and urobilinogen. April 21st, twenty-three days after splenectomy, the hemoglobin was 69 per cent., erythrocytes 3,140,000, color index 1+, leukocytes 6700, polynuclear neutrophils 50.3 per cent., small lym-

phocytes 34 per cent., large lymphocytes, 7.7 per cent., eosinophils 6.7 per cent., basophils 1.3 per cent., normoblasts 1.

Three months after the operation the patient was doing a little light housework and was steadily gaining. Her color was good, her complexion rosy, and there was no icterus. The hemoglobin was 75 per cent., erythrocytes 3,810,000; 2 normoblasts were seen. The urine contained urobilin, but no urobilinogen.

Nine and one-half months after operation the patient reported that she had contracted a diarrhea which was epidemic in her town at that time. This weakened her considerably. Her mouth was not sore; there was no numbness or tingling of the extremities; her color was still good. The liver margin was just palpable. Urobilin was present in the urine at the time of one examination and absent at another; urobilinogen was absent. Courses of iron and arsenic treatment were continued.

Three months later, April 9th, the hemoglobin was 70 per cent., erythrocytes 3,840,000, leukocytes 9200, polynuclear neutrophils 37.3 per cent., small lymphocytes 49.7 per cent., large lymphocytes 9.7 per cent., eosinophils 3 per cent., basophils 0.3 per cent., normoblasts 23.

One year and eight months after operation, November 21st, the hemoglobin was 73 per cent., erythrocytes 4,000,000, leukocytes 7200, polynuclear neutrophils 56 per cent.; normoblasts 9. In the spring of 1918 a respiratory infection and subsequent hot weather weakened the patient considerably. Her color remained good, although the blood June 7th showed only 53 per cent. hemoglobin, erythrocytes 2,190,000, leukocytes 9000, of which 62.3 per cent. were polynuclear neutrophils, normoblasts 85. Her liver was doubtfully enlarged. She was given iron and arsenic and again improved.

July, 1919, the patient reported in rather poor condition, which had begun to improve only during the preceding few weeks. Her strength, however, had continued to be quite good, and she had been able to do light housework all this time. August 8th the hemoglobin was 38 per cent., erythrocytes 1,520,000, leukocytes 19,000, polynuclear neutrophils 14 per cent., small lympho-

cytes 82 per cent., large lymphocytes 1 per cent., eosinophils 1 per cent., neutrophilic myelocytes 2 per cent., normoblasts 710. One month later the hemoglobin was 36 per cent., erythrocytes 1,060,000. No transfusion was advised and medical support was continued, the shower of normoblasts being considered as a possible preliminary to spontaneous improvement in the blood. The patient improved somewhat, and at her last visit, October 20th, the red cell count was 1,480,000, with 337 normoblasts.

The course of this second case during the three years and six months which have elapsed since operation presents a somewhat different reaction to splenectomy from that of Case I. It would seem that in the removal of the spleen the major part of the hemolytic factor was removed, in contrast to the first case, in which probably only a fraction of it was removed. The rapid improvement in the blood was thereby made possible in spite of the fact that the bone-marrow may have been somewhat less responsive than in Case I. No shower of blasts was observed until three years after operation, and the few normoblasts persistently present suggest rather a doggedly courageous though considerably damaged bone-marrow. The patient's condition again improved, although she did not regain her previous good level. It would seem that the downward course observed in this case during the past year is the result of a gradually lessening blood-producing activity rather than of very excessive blood destruction.

After scrutiny of the course of our 50 patients splenectomized for pernicious anemia we are unable, thus far, to advance any chain of reasoning to explain their different reactions to splenectomy. Even the course of the 2 patients herein described presents more definite features than are usually found. Sex, age, previous infections, the duration and severity of the disease, degree of anemia, hemolytic activity, diarrhea and other gastrointestinal disturbances, involvement of the central nervous system, the size of the liver and spleen, and so forth, are being traced in the hope of identifying cases favorable for operation, and especially of obtaining additional light on the etiology of the

disease. Thus far our efforts have not led to any definite conclusions.

BIBLIOGRAPHY

1. Giffin, H. Z., Sanford, A. H., and Szlapka, T. L.: The Estimation of Urobilin and Urobilinogen in the Duodenal Contents, Amer. Jour. Med. Sci., clv, 562–579, May, 1918.
2. Schneider, J. P.: The Splenic Pathology of Pernicious Anemia and Allied Conditions. A Duodenal Method of Estimating Hemolysis, Arch. Int. Med., xvii, 32–41, January, 1916.

SOME DATA ON THE RANGE OF LIFE OF TRANSFUSED BLOOD-CORPUSCLES IN PERSONS WITHOUT IDIOPATHIC BLOOD DISEASES.

WINIFRED ASHBY, M. S.

IN a previous publication I showed that the transfused red blood-corpuscle does not have a transitory existence in the body, but that it remains in the blood-stream for a considerable length of time. The method used to show this is dependent on the iso-agglutinins present in blood and is based on the fact (which I demonstrated with in vitro mixtures of blood corpuscles) that corpuscles belonging to two different blood groups if mixed can be separated quantitatively from one another by treating with a serum that will differentially agglutinate the corpuscles of one kind, leaving the others free. This method applies equally well to in vivo mixtures; the transfused blood-corpuscles in a patient can be separated from the recipient's native corpuscles by differentially agglutinating the recipient's corpuscles with appropriate serum, provided the donor and recipient are in different groups. This method is only applicable, of course, to cases in which patients belonging to Groups I, II, or III (Moss's nomenclature) are transfused with Group IV blood, or in which patients belonging to Group I are transfused with Group II or Group III blood, but in these cases the history of the transfused blood can be followed readily.

Any one accustomed to using the modified Moss's method of blood grouping will probably have, when he thinks of agglutinated corpuscles, a mental picture of clumps with varying quantities of free corpuscles floating between them. This picture is one given with serum diluted with at least one-half its volume of salt solution and with a varying proportion between corpuscles and serum. When a sufficiently large amount of

undiluted serum is used and the mixture is incubated, however, this picture is changed; an almost complete agglutination of the corpuscles is uniformly obtained, a few corpuscles only lying free between the clumps. Figure 157 illustrates such an agglutination, the count in this case being 0.05 million for each cubic millimeter of blood used. The degree of completeness of the agglutination varies somewhat with different bloods; the count

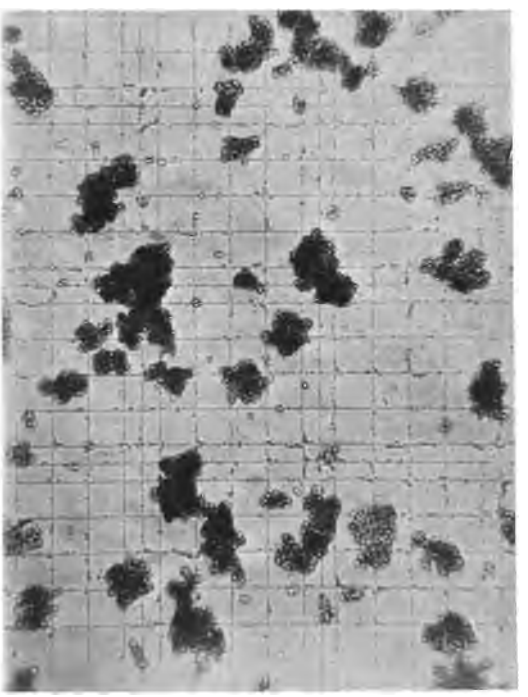


Fig. 157.—Photomicrograph of Group II blood treated with agglutinating serum.

of the free corpuscles will usually range from 0.02 to 0.08 million for each cubic millimeter, rarely going above 0.1 million for each cubic millimeter. In two cases of jaundice the blood-count was considerably higher. When unagglutinable corpuscles, however, are previously added to agglutinable corpuscles, either in the test-tube or by transfusion, the number of corpuscles still free after agglutination jumps conspiciously, and we have the pic-

ture illustrated by Fig. 158 (the agglutinated blood of a Group II patient who had received a 1200 c.c. transfusion of Group IV blood) or by Fig. 159 (the agglutinated blood of a Group II patient transfused with 500 c.c. of Group IV blood).

The accurate interpretation of the quantitative difference between the free corpuscles in these two instances becomes a

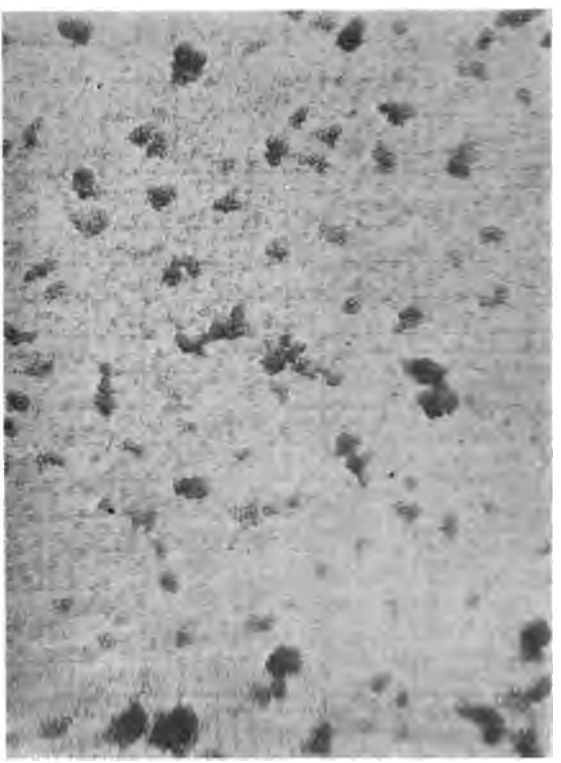


Fig. 158.—Photomicrograph of agglutinated blood of a Group II patient. Sixteen days after he has received a 1200 c.c. transfusion of Group IV blood clumped corpuscles and free Group IV corpuscles are present in large numbers.

matter of interest. The question arises as to whether or not the unagglutinable corpuscles appear quantitatively as free corpuscles. The other alternatives would be that the unagglutinable corpuscles might be caught in the clumps, in which case there would be fewer free corpuscles than there were unagglu-

tinable corpuscles added; or it might be that the presence of the unagglutinable corpuscles would, to a certain extent, inhibit agglutination, in which case there would be an excess of free corpuscles. To test this, mixtures of Group IV and Group II blood were made by the drop method in the proportions of 1: 30, 1: 15, 1: 10, 1: 6, 1: 4, and 1: 3. Dilutions of 1: 22 were made of these mixtures with Group IV citrated serum with the white

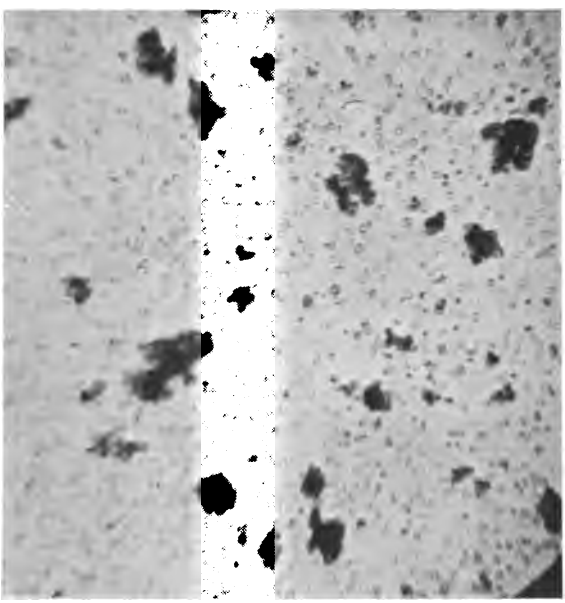


Fig. 159.—Photomicrograph of agglutinated blood of a Group II patient who had received a 500 c.c. transfusion of Group IV blood. Clumped corpuscles and free Group IV corpuscles are present in moderate numbers.

cell diluting pipet; the dilutions were expelled into small tubes and incubated forty minutes, agitated at ten-minute intervals. Two tests were made from each mixture and counts of the unagglutinated cells were made from each in the red blood-cell counting chamber. These were averaged, and, after subtracting the number of unagglutinated corpuscles found in the straight Group II blood, which in this instance was unusually high, 0.12 million for each cubic millimeter, the number obtained was

compared with the number of Group IV corpuscles computed to be present. The latter number was found in each case by taking a percentage of the whole Group IV blood count equal to the percentage of Group IV blood in the mixture. The results were as follows:

TABLE I

Proportion of Group IV corpuscles mixed with Group II corpuscles.	Unagglutinated corpuscles per cubic millimeter minus 120,000.	Calculated number of Group IV corpuscles per cubic millimeter.
1 : 30	127,370	137,000
1 : 15	228,570	267,000
1 : 10	391,600	388,100
1 : 6	572,773	610,000
1 : 4	803,559	854,000
1 : 3	1,035,320	1,067,500

It will be seen from Table I that the unagglutinated corpuscles appear quantitatively as free corpuscles. Not only is it true that the appearance of excessive numbers of free corpuscles is an indication that Group IV corpuscles are present, but it is also true that a count of these corpuscles tells how much Group IV blood is present.

The technic which I originally used in applying this method to the patient is as follows: Blood is taken from the ear in a white cell counting pipet to the 0.5 mark; the pipet is then filled to the 11 mark with the agglutinating serum, to which a 4.4 per cent. of citrate solution has been mixed in the proportion of 20 : 1, and the whole is expelled into a small test-tube and shaken, thus giving a 1 : 22 mixture of blood and citrated serum. This mixture is incubated at 37° C. for forty minutes, agitated every ten minutes, and left in the ice-box over night. The mixture is then shaken enough to insure an even suspension, a drop of it is placed in the red blood-counting chamber, and the count of the unagglutinated corpuscles is made. One hundred and sixty squares are counted and the count is mutiplied by $\frac{11 \times 100}{2}$ to give the number of unagglutinated corpuscles for each cubic millimeter of blood. The 11 factor is used instead of the 10 factor, which appears in the usual use of the white counting pipet, because in

expelling the mixture into the test-tube the dilutent present in the graduated tube of the pipet is added to that in the bulb. I have since made a slight modification in this technic; I do not now incubate over night in the ice-box. This was discontinued because on using a more efficient ice-box I was troubled with false agglutination from the cold. I now simply allow the tubes to stand for about fifteen minutes at room temperature after removing them from the incubator, and then make the count.

The degree of accuracy to which these counts can be made is fully equal to the ordinary red blood-corpuscle count; there are more factors of error, however, in preparing for the count. The serum used for agglutination must be centrifuged until microscopic examination shows it to be free from corpuscles. The serum must be potent as far as agglutinating properties are concerned; to make sure of this it is well to run a control on blood of an agglutinable group. If the serum happens to be hemolytic toward the agglutinable corpuscles, the count will be too high because the clumps are broken by their partial hemolysis and the more resistant corpuscles freed. It is not often that a serum also hemolyzes corpuscles which it agglutinates, but some serums seem to be hemolytic toward more bloods than others. If a clean hemolysis of the agglutinated corpuscles takes place, an accurate count of the unagglutinable corpuscles can be made, but this rarely happens. In one instance in which it occurred the count of resistant corpuscles was 640,000, whereas the count of unagglutinated corpuscles made four hours previously, using non-hemolytic agglutinating serums, was 647,000. If the free corpuscles are too thick from which to make an accurate count, it is possible to dilute the mixtures with serum by mixing equal numbers of drops of each. When the clumps are once formed by a non-hemolytic serum they are stable; there is no danger that the amount of shaking necessary to obtain an even suspension may cause an increase in the count of the free corpuscles.

More than 70 patients transfused by this method have been studied. The majority of the patients had pernicious anemia; their cases will be discussed in a later paper. Since many of the patients in the Mayo Clinic come from a distance, and

return to their homes as soon as they are convalescent, it is only rarely possible to study the history of a blood transfusion to its finish. The average stay of patients is from two to three weeks, whereas six to eight weeks, and sometimes more, are needed for a satisfactory determination of the end-point. The study of these 70 patients bears out my original finding based on 3 cases, namely, that the transfused blood remains in the blood-stream. The brief abstracts of 10 protocols are given as being more nearly representative of the elimination of the transfused blood than any outside of the pernicious anemia group.

CASE I.—A woman aged thirty-five, whose normal weight was 140 pounds, and present weight 138, had been operated on for fibroid of the uterus. September 21, 1918, the unagglutinated cells were 88,000 for each cubic millimeter; the blood count could not be obtained. Seven hundred cubic centimeters of Group IV blood were given because of severe hemorrhage; the hemorrhage continued and an additional 500 c.c. of Group IV blood were given.

1918	Red blood-corpuscles for each cubic millimeter.	Unagglutinated corpuscles for each cubic millimeter.
September 23	3,800,000	1,412,400
" 25	3,720,000	
" 27	4,090,000	
" 30		1,293,800
October 2	4,920,000	
" 4	4,405,000	
" 7	4,000,000	870,100
" 10	4,060,000	737,000
" 12	4,250,000	702,900
" 15		796,400
" 19	4,550,000	299,200
" 25	4,109,000	118,800
" 30	4,302,000	51,700

CASE II.—A Group II person, aged thirty-two, had a secondary type of anemia, possibly from hemorrhage due to piles. The patient's normal weight was 160 pounds, the present weight was 135 pounds. October 1, 1918, the red blood-cells were 2,100,000; the unagglutinated cells were 1100 for each cubic

millimeter. A transfusion was done with 500 c.c. of Group IV blood.

1918	Red blood-corpuscles for each cubic millimeter.	Unagglutinated corpuscles for each cubic millimeter.
October 12	2,820,000	409,200
" 14	2,550,000	
" 15		318,000
" 17	2,705,000	390,700
Mild attack of influenza.		
" 21	2,600,000	333,700
" 24	2,660,000	367,400
" 25 Patient sent home for two weeks.		
November 9	2,510,000	251,020
" 10		260,700
" 12	2,105,000	258,720
" 13	2,185,000	246,070
A transfusion was done of 500 c.c. of Group IV blood.		
" 14	2,625,000	585,200
" 20	2,760,000	517,000

CASE III.—A woman aged thirty-three, with a normal weight of 100 pounds, rather pale and emaciated, had been given a diagnosis of pelvic tumor. This patient was in Group II, and received transfusion from a Group II donor October 26, 1918, and a 500 c.c. transfusion from a Group IV donor November 11, 1918; November 15th a subtotal abdominal hysterectomy, left oöphorectomy, and salpingectomy were performed. The patient's convalescence was satisfactory.

1918	Red blood-corpuscles for each cubic millimeter.	Unagglutinated corpuscles for each cubic millimeter.
November 11	4,050,000	42,000
" 11	Transfusion	
" 11	3,970,000	478,000
" 15	Hysterectomy	
" 25	4,580,000	436,000
" 29	4,780,000	385,000
December 5	4,770,000	404,000
" 9	4,520,000	321,000
" 11		164,000
" 13	4,650,000	163,000
" 17	4,800,000	132,000

CASE IV.—A woman aged forty-five, whose weight was 87 pounds, was found to have a common duct obstruction and hepatitis, syphilis 3. This patient was in Group II, with a coagulation time of 13. December 27, 1918, a 500 c.c. transfusion of Group IV citrated blood was administered. December 28th choledochotomy and cholecystostomy were performed.

1918	Red blood-corpuscles for each cubic millimeter.	Unagglutinated corpuscles for each cubic millimeter.
December 27	3,360,000	154,000
" 27	500 c.c. Group IV transfusion.	
" 27	3,250,000	663,000
" 31		670,000
1919		
January 2	3,730,000	
" 6	4,030,000	583,000
" 9	4,500,000	687,000
" 11	4,140,000	
" 14		590,000
" 17		585,000
" 21		479,000
" 23		409,000
" 25	3,940,000	418,000
" 28	3,870,000	519,000
" 31	4,080,000	333,000
February 3	4,070,000	177,000

CASE V.—A man aged thirty-two, whose weight was 103 pounds, had duodenal ulcer and chronic appendicitis. December 23, 1918, the hemoglobin was 76 per cent. December 27th a posterior gastro-enterostomy and appendectomy were performed followed by transfusion of Group IV citrated blood.

1918	Red blood-corpuscles for each cubic millimeter.	Unagglutinated corpuscles for each cubic millimeter.
December 27 Transfusion with 500 c.c. Group IV citrated blood.		
" 31		500,000
1919		
January 7		521,000
" 11	3,165,000	
" 18	4,300,000	551,000

CASE VI.—A man aged forty-two, whose weight was 167, had cholocystitis, obstructive jaundice, and chronic nephritis. This patient was in Group I, his coagulation time was eighteen

minutes. December 30, 1918, 500 c.c. of citrated Group I blood were transfused. December 13th choledochotomy and cholecystostomy were performed. January 7, 1919, the patient had a hemorrhage, and transfusion was given of 500 c.c. Group IV citrated blood. A satisfactory convalescence followed.

1918	Red blood-corpuscles for each cubic millimeter.	Unagglutinated corpuscles for each cubic millimeter.
December 30 Transfusion with Group IV serum.		
1919		
January 9		623,000
" 11	3,280,000	
" 14		568,000
" 17	3,310,000	563,000
" 25	3,700,000	
" 27	4,420,000	449,000
" 31	3,700,000	434,000
February 3	4,170,000	334,000
" 6		
" 8	4,200,000	339,000

CASE VII.—A woman aged thirty-two, whose weight was 133 pounds, and in good general health, had multiple lipomas and von Recklinghausen's disease. February 25, 1919, large lipomas were removed from the left buttock and arm. February 26th the patient had a hemorrhage and was transfused with 500 c.c. of Group IV citrated blood. March 22d protruding internal hemorrhages were sutured, and March 31st multiple smaller lipomas were excised. The patient's convalescence was excellent.

1919	Red blood-corpuscles for each cubic millimeter.	Unagglutinated corpuscles for each cubic millimeter.
February 26 Transfusion.		
March 3	2,950,000	759,000
" 7	2,920,000	731,000
" 10	2,940,000	
" 18	3,670,000	686,000
" 21	3,070,000	600,000
" 24	3,750,000	553,000
" 27	4,000,000	474,000
" 30	4,290,000	489,000
April 1	4,110,000	545,000
" 4	4,300,000	242,000
" 10	4,000,000	220,000

CASE VIII.—A woman aged thirty-nine had exophthalmic goiter and secondary anemia of long standing. April 29, 1919, the metabolic rate was +25; red blood-cells 4,590,000; hemoglobin 40 per cent.; color index 0.4+. This patient was in

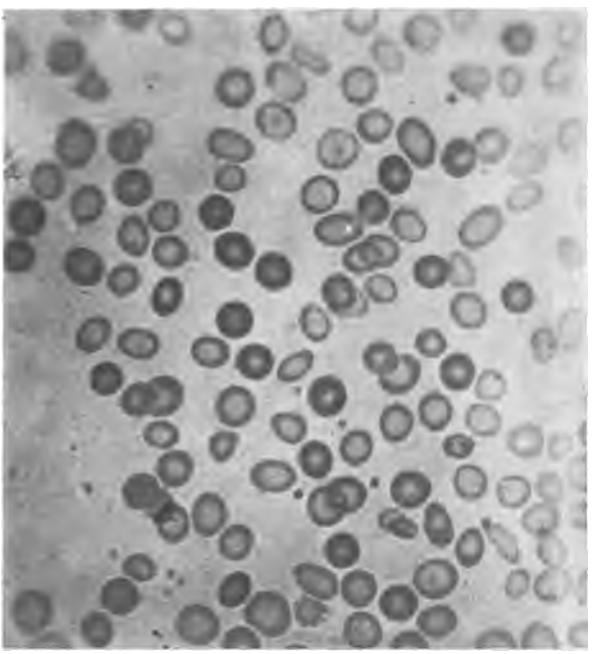


Fig. 160.—Photomicrograph of a blood-smear from a patient (Case VIII) whose initial color index was 0.4+ taken May 19th after the second transfusion. The dark corpuscles are apparently the normal transfused corpuscles.

Group II and received two transfusions: one May 2d, when a Group IV donor was used, and one May 19th, when a Group II donor was used. June 9th partial thyroidectomy was done, and June 26th the metabolic rate had dropped to normal. The patient made a complete recovery.

1919	Red blood-corpuscles for each cubic millimeter.	Unagglutinated corpuscles for each cubic millimeter.	Hemoglobin, per cent.
May 2	4,590,000	12,000	
" 2 Transfusion of 500 c.c. Group IV citrated blood.			
" 2	4,470,000	552,000	50
" 4	5,640,000		
" 7	5,970,000	495,000	
" 14	4,730,000	428,000	46
" 16	4,930,000	466,000	
" 19	4,550,000	449,000	43
" 19 Transfusion of 500 c.c. of Group II blood (Fig. 160).			
" 19	5,850,000	411,000	52
" 20	5,150,000	380,000	
" 22	5,220,000		55
" 31	5,500,000	385,000	61
June 3	5,540,000	367,000	56
" 7	4,940,000		
" 8	5,400,000		
" 9	5,770,000	302,000	70
" 14	5,140,000		70
" 19		407,000	
" 23	6,640,000	281,000	70
" 28	6,360,000	220,000	59

CASE IX.—A man aged fifty, a farm laborer of powerful build, was examined April 1, 1919, at which time the hemoglobin was 84 per cent. April 10th a choledochotomy, cholecystectomy, and appendectomy were performed. April 17th secondary anemia became apparent and he was transfused with 500 c.c. of Group IV citrated blood. April 29th a herniotomy was performed, after which the patient made an uneventful recovery.

1919	Red blood-corpuscles for each cubic millimeter.	Unagglutinated corpuscles for each cubic millimeter.
April 29	4,400,000	393,000
May 7	4,500,000	331,000
" 9	4,670,000	371,000
" 13		362,000
June 5	4,830,000	254,000
" 7	5,150,000	233,000
" 24	5,580,000	210,000

CASE X.—A man aged thirty-three, weighing normally 129 pounds, and slightly emaciated, had had an abscess of the left kidney which had been drained twelve years before. Since then he had had a discharging sinus. *x*-Ray examination showed stones in the left kidney. June 6, 1919, these were removed. June 7th a hemorrhage occurred and 510 c.c. of citrated blood of Group IV were transfused. An uneventful convalescence followed.

1919	Red blood-corpuscles for each cubic millimeter.	Unagglutinated corpuscles for each cubic millimeter.
June 7	4,930,000	996,000
" 8	3,120,000	600,000
" 16	3,530,000	626,000
" 19	3,670,000	623,000
" 25	3,450,000	502,000
" 26		448,000
July 12[1]		18,000

In 6 of these cases transfusion was done because of hemorrhage after operation. In 4 transfusion was done before operation, with no subsequent hemorrhage. In the cases in which transfusion was done after hemorrhage the initial count of transfused corpuscles, when the amount of blood given and the body weight of the patient was taken into consideration, was found to be high in comparison with the initial counts obtained in the 4 cases in which transfusion was done before operation with no subsequent hemorrhage. This high initial count is due to low blood volume, the corpuscles of the transfused blood being less highly diluted than would be the case in patients with a normal blood volume. The count falls more or less slowly because of increase in blood volume; it then may remain on a level for some time, after which there will be a fall due to the elimination of blood-corpuscles. The recovery of normal blood volume and the consequent drop in the count of transfused blood is sometimes surprisingly slow. This, however, tallies with the findings of Robertson and Bock: "Blood volume tests made on a number of soldiers recovering from hemorrhage have shown that in many instances dilution of the blood occurs very slowly. The prin-

[1] This count was kindly made for us by the patient after he returned home

cipal reason for this seems to be (*a*) an initial lack of fluid of the tissue, (*b*) absence of any subsequent attempt of the body to make up this fluid." The authors cite 1 case in which the patient had a blood volume of 2723 c.c. before transfusion and showed an increase in volume to only 3886 c.c. eight days afterward, whereas for a man of 70 kilos it should be about 6000 c.c.

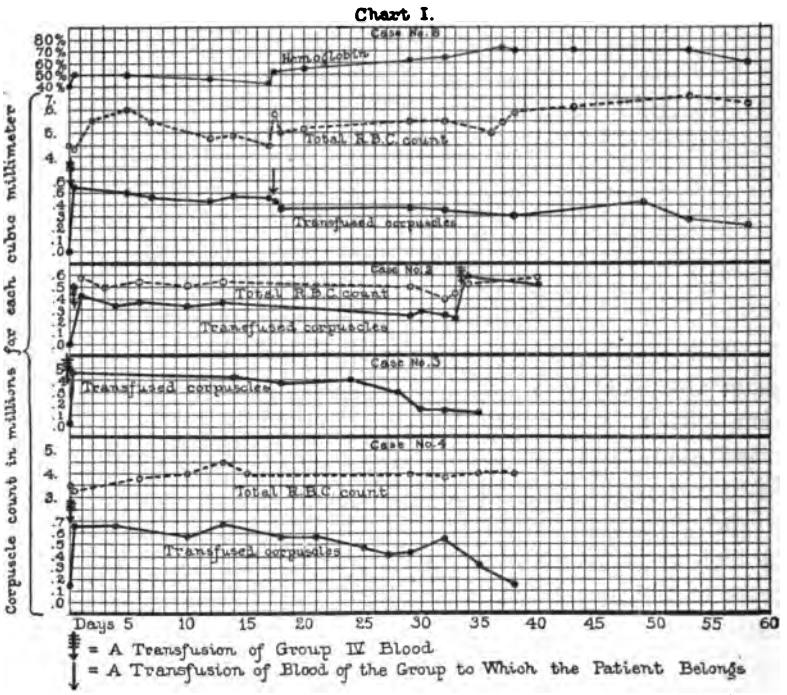


Chart I.
Case No. 6
Hemoglobin
Total R.B.C. count
Transfused corpuscles
Case No. 2
Total R.B.C. count
Transfused corpuscles
Case No. 3
Transfused corpuscles
Case No. 4
Total R.B.C. count
Transfused corpuscles
Corpuscle count in millions for each cubic millimeter
Days 5 10 15 20 25 30 35 40 45 50 55 60
= A Transfusion of Group IV Blood
= A Transfusion of Blood of the Group to Which the Patient Belongs

Fig. 161.—The rate of disappearance of transfused Group IV blood in 4 patients who did not have hemorrhage.

It is obvious that with the injection of red blood-corpuscles of a known number for each cubic millimeter the dilution of which can be determined after injection from the count of unagglutinable corpuscles in the transfused blood, we have a method of estimating blood volume. The general principle of this is the same as that of Keith, Rountree, and Geraghty's neutral red method, and of Meek and Gasser's method with gum acacia; and the method as a whole is very similar to one devised by Todd, based on isohemolysis, which is applicable to measurement

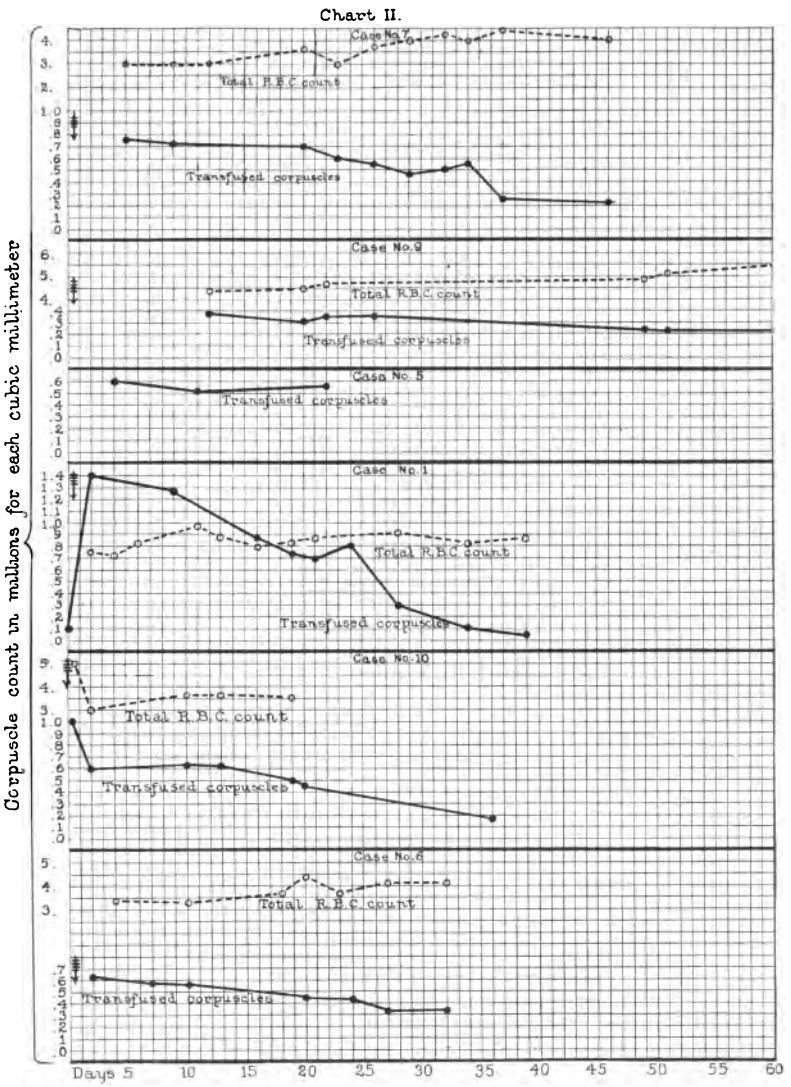


Fig. 162.—The rate of disappearance of transfused blood in patients who were transfused because of hemorrhage and in some of whom there was subsequent increase in blood volume.

of blood volume in cattle. From a proportion between the unknown blood volume, the known quantity of blood injected, the corpuscle count of the injected blood, and the count of trans-

fused corpuscles in the recipient's blood, a figure for the blood volume can be obtained. The account of the results in general obtained by this method and an estimate of its value will be given in a later paper. Using from 7.5 to 8.5 per cent. of the body weight as normal volume, although 7.5 per cent. is probably too low, in the cases after hemorrhage in which there was a low initial blood volume I have calculated at what date the dilution of the transfused blood-corpuscles indicated normal blood volume, and have assumed that any decrease in the count of unagglutinable corpuscles beyond this point is due to a destruction of the transfused blood. The error in this procedure lies in the fact that the transfused blood-corpuscles may have been destroyed at the same time that they were diluted. The estimated point at which the blood volume becomes normal, if such is the case, would be reached sooner than it is in reality; but, judging from the rate of fall of the other curves which represent the cases in which there was no hemorrhage and an approximately normal initial blood volume, I consider this error to be negligible in this connection.

I have estimated by this plan the length of time in each case during which the elimination of transfused corpuscles was no more than 10 per cent., the length of time during which only 80 to 60 per cent. of the transfused corpuscles remained, and the length of time during which only 50 to 40 per cent. remained. The results as given in Table II claim to be no more than a rough summation of the preceding curves:

Case.	Sex.	Age.	More than 90 per cent. of transfused corpuscles remaining after	From 80 to 60 per cent. of transfused corpuscles remaining after	From 50 to 40 per cent. of transfused corpuscles remaining after
1	F.	35	24 days	26 days	28 days
2	F.	32	12 "	33 "	?
3	F.	32	14 "	28 "	29 "
4	F.	45	21 "	32 "	34 "
5	M.	32	22+ "	?	?
6	M.	42	24 "	32 "	?
7	F.	32	34 "	35 "	46 "
8	F.	39	17 "	32 "	52 "
9	M.	50	26 "	35 "	
10	M.	33	20+ "	30 "	

The time during which there was no considerable change in the curve other than attributable to dilution of the transfused corpuscles by increased blood volume ranged from fourteen to thirty-four days, with an average of more than twenty-one days. The time during which from 80 to 60 per cent. of the transfused blood remained was from twenty-six to thirty-five days, with an average of thirty-one. The length of time after which 50 to 40 per cent. of the transfused blood remained ranged from twenty-eight to fifty-two days; the average would doubtless be found to be more than thirty-seven days if all the curves had been taken for a sufficient length of time. The rate at which transfused blood is eliminated in these 10 nearly normal persons varies considerably, but the series is too short to give any indication of the factors which affect this rate.

BIBLIOGRAPHY

1. Ashby, W.: The Determination of the Length of Life of the Transfused Blood-corpuscles in Man, Jour. Exper. Med., xxix, 267–281, March 1, 1919.
2. Keith, N. M., Rountree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med., xvi, 547–576, October, 1915.
3. Meek, W. J., and Gasser, H. S.: Blood Volume, a Method for its Determination with Data for Dogs, Cats, and Rabbits, Amer. Jour. Physiol., xlvii, 302–317, December 1, 1918.
4. Moss, W. L.: Studies on Iso-agglutinins and Isohemolysis, Johns Hopkins Hosp. Bull., xxi, 63–70, March, 1910.
5. Roberston, O. H., and Bock, A. V.: Blood Volume in Wounded Soldiers. II. The Use of Forced Fluids by the Alimentary Tract in the Restoration of Blood Volume after Hemorrhage, Jour. Exper. Med., xxix, 155–171, February, 1919.
6. Todd, C., and White, R. G.: On the Fate of Red Blood Corpuscles when Injected into the Circulation of an Animal of the Same Species, with a New Method for the Determination of the Total Volume of the Blood, Proc. Roy. Soc., London, lxxxiv, Ser. B., 255–259, July 1, 1911.

BLOOD TRANSFUSION: INDICATIONS FOR ITS USE; METHODS OF SELECTING DONORS; AND A BRIEF CONSIDERATION OF TECHNIC

A. H. SANFORD, M. D.

DURING the last few years the transfusion of blood has become a very popular therapeutic measure. Simple methods, such as the use of blood decalcified with sodium citrate, make it possible for anyone to learn easily the necessary technic. There is perhaps a tendency at the present time, however, to overestimate the benefits to be derived from this procedure. Transfusion should not be regarded as a form of intravenous medication. There is a certain amount of risk to the patient that must be realized by the surgeon, and the indications for its use must be sufficiently evident to induce him to assume the responsibility of this risk. There are at least five well-recognized conditions in which blood transfusion has been employed with some degree of success:

1. Replacing the blood volume following hemorrhage. Military surgeons have performed the operation many times for this purpose. If the patient is in shock, particularly if the systolic blood-pressure is below 90, the transfusion is an emergency procedure and must be carried out with the least possible delay. The opportunities for applying this method in such cases are not met with often in civil practice.

2. Replacing blood lost by disease, especially in pernicious anemia, the most common application of the measure. Winifred Ashby has shown that the red blood-corpuscle probably lives longer than was formerly believed, and that transfused blood may stay in the patient's veins for a number of days, even as long as one month. Accordingly, even the small amount of blood transfused, particularly if the patient receives two or three

transfusions during the month, may furnish healthy corpuscles which will functionate in place of those that have been destroyed. Some forms of severe secondary anemia also may be benefited by this form of treatment, but the question must be considered whether or not some other method of stimulating blood production may not be advisable, even though the results will not be obtained so rapidly as with the transfusion method.

3. Stimulation of the hematopoietic system, apparently another effect of blood transfusion. It is undoubtedly true that many patients continue to improve after a series of transfusions long after the temporary effect of the added blood must have disappeared from the circulatory system.

4. Rapid alteration of the factors of coagulation by adding thromboplastic material. This is an exceedingly important function. In hemophilia the coagulation time and bleeding time may be so changed that minor operations may be carried out with impunity. In jaundice, in which calcium is lacking in the blood, in addition to the changing of the coagulation time by the administration of calcium lactate by mouth, preoperative transfusion safeguards the patient against the tendency to oozing from small vessels which is so apt to occur.

5. The transference of antibodies from a donor supposed to be immune to some definite organism, a somewhat doubtful use for transfusion. Various patients with postinfluenzal pneumonia have been treated by transfusion with blood of donors that have recovered from this disease. Our limited experience with this form of treatment yielded negative results. There is a possibility, however, that in well-selected instances true passive immunity may be rapidly instituted by this form of treatment. Transfusion has also been used in cases of general sepsis, but it is very doubtful whether any true benefit should be expected from the procedure.

The dangers of transfusions lie, chiefly, in the selection of the donor.[11] In the first place, the possibility of transmitting disease must be considered carefully. With the possible exception of the use of a husband for the wife, or a wife for the husband, as a donor in emergencies, no one should be used as a donor without

first having a serologic examination of the blood for evidence of syphilis. If possible, careful physical examination should be made, and the person's social status judiciously considered. Professional donors are usually not hard to obtain. Healthy housewives whose reputations are well known in the community in which they live usually make excellent donors. Industrious men, preferably married and known to have no bad habits, may be readily found for the purpose in most communities. As a general rule, persons past middle life and young boys anxious to obtain "easy money" should not be placed on the list of professional donors. There is also the possibility of transmitting other diseases besides syphilis, although no such authentic instances have come to our attention.

The chief concern of the surgeon should be the knowledge that the donor's corpuscles are compatible with the serum of the recipient. He should be assured, either by his own examination or by those responsible for the selection of donors, that the patient's serum will not agglutinate the donor's corpuscles.

Agglutination of human corpuscles by human serum or isohemagglutination is in itself a most interesting biologic phenomenon deserving of consideration on the part of any physician. All persons may be placed in one of four groups according to whether or not they have in their serum iso-agglutinins of a certain type. Strangely enough, all the lower animals we have studied, or those we have seen reported in the literature, cannot be thus definitely grouped. The phenomenon of the agglutination of the human corpuscles by human serum was first noticed in pathologic conditions, and was thought, at one time, to be peculiar to certain diseases. Landsteiner was the first investigator to point out that iso-agglutination is not a pathologic phenomenon, but of a biologic character. He discovered three distinct groups. He did not find the fourth group, Moss's Group I. Moss and Ottenberg, working independently, discovered that persons can be classified in four groups. Moss has priority of publication and his classification is now used generally. Ottenberg's classification is practically the same except that his Group IV is the Moss Group I, and vice versa.

Figure 163 shows the relation of the four groups.[12] By means of the parallelogram it is clear that the relation of one group to the other three may be pointed out either by the laterals or diagonals. The corpuscles of the various groups are agglutinated by the serums of the groups from which the arrows lead. Group I persons contain no agglutinin in their serum, which is evident by the fact that no arrows lead away from this group and all lead toward it. Corpuscles of this group are agglutinated

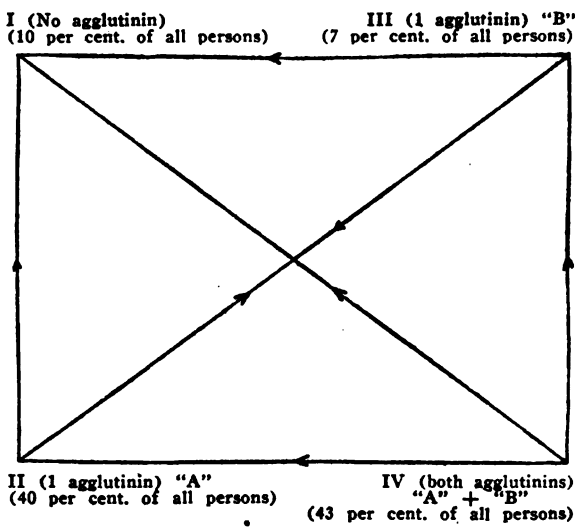

I (No agglutinin)
(10 per cent. of all persons)
III (1 agglutinin) "B"
(7 per cent. of all persons)
II (1 agglutinin) "A"
(40 per cent. of all persons)
IV (both agglutinins)
"A" + "B"
(43 per cent. of all persons)

Fig. 163.—Moss agglutination groups: The corpuscles of the various groups are agglutinated by the serums of the groups from which the arrows lead.

by serums of the other three. Group IV is just the opposite. The serum from this group agglutinates the corpuscles of all the other three groups, but the corpuscles of this group are not agglutinated by the serum of any group. Groups II and III are in reciprocal groups and are incompatible with each other. Notice that the arrows on the diagonal leading from Group II to Group III point in both directions. The serum of Group II agglutinates the corpuscles of Group III and the serum of Group III agglutinates the corpuscles of Group II. The corpuscles of

Groups I, II, and III are agglutinated by the serum of Group IV. An explanation for this phenomenon based on Landsteiner's hypothesis is plausible. Landsteiner did not find Group I, the group in which the serum contained no agglutinins. He stated, however, that there are persons who have in their serum iso-agglutinins which he called "A." This agglutinin in their blood protects their corpuscles from agglutinins of this type. Thus the "A" blood is protected from the "A" agglutinin in other blood. Group "B" serum will agglutinate corpuscles of all groups except those containing "B" agglutinin. The corpuscles of Group IV, Landsteiner's third group, are not agglutinated because they are protected by having both "A" and "B" agglutinins in the serum. In like manner Group I may be explained, since this group contains no agglutinins. Corpuscles of this group are agglutinated by either "A" or "B," or by both "A" and "B," of Group IV serum.

The percentages of persons in the various groups are of interest. Moss studied 100 persons in series of 20 each. According to his figures, 10 per cent. of all persons are in Group I, 40 per cent. in Group II, 7 per cent. in Group III, and 43 per cent. in Group IV. Our figures are of interest in comparison with those of Moss. Two years ago we found, in going over our statistics of a little less than 1000 persons, that 5.09 per cent. of all persons were in Group I, 42.42 per cent. were in Group II, 8.8 per cent. were in Group III, and 43.69 per cent. were in Group IV. To the present time we have made practically 3000 groupings, and our average figures are 4.5 per cent. in Group I, 42.3 per cent. in Group II, 8.7 per cent. in Group III, and 44.5 per cent. in Group IV. These figures are of interest in showing that although Moss tested a comparatively small number of persons, he undoubtedly discovered the proper law of grouping.

Methods for Determining the Compatibility of Donor's and Recipient's Blood.—The first method used for the determination of the compatibility of a prospective donor's corpuscles for the recipient's serum was a macroscopic test. A corpuscle suspension is made of the washed corpuscles of both donor and patient.

The serums of both donor and patient are also used. In a Wassermann tube 3 drops of an approximate 5 per cent. suspension of washed corpuscles of the patient are placed with 9 drops of the donor's serum. In another tube in like manner 3 drops of the donor's corpuscles are placed with 9 drops of the recipient's serum. They are then incubated for two hours at 37.5° C. Every few minutes the tubes are well shaken and are observed for the presence of agglutinins and for any trace of hemolyis. The tubes should be placed in the ice-box after two hours and left over night. The final reading is made the next day. In case of emergency a report may be made within a few hours, omitting the over night ice-box procedure, basing the report entirely on the macroscopic appearance of the cells in the test-tube. This is an excellent method and is still employed in some hospitals; it is time-consuming, however, and usually some of the more rapid microscopic methods are preferred. A number of methods, differing from each other only slightly in technic, are reported by various workers.

The Brem Method of Grouping.—The Brem method is employed at the Mayo Clinic, and has been found exceedingly satisfactory in our series of cases.[13] The apparatus required is a microscope, hollow ground, hanging-drop slides, cover-slips, a loop of nichrome, or platinum wire, a few small Wassermann tubes, and a 2 per cent. sodium citrate solution. It is necessary to have on hand serum and fresh corpuscle suspension of either Group II or Group III. If a large series of tests is being made it is always possible to have these known bloods on hand by keeping the Group II and the Group III bloods as they appear from day to day. The corpuscle suspensions soon autolyze, and if it is not possible to keep these on hand, usually some person in the laboratory will be found to be in either Group II or Group III, and his blood may be used for testing unknowns. The person's blood to be tested is obtained by venipuncture preferably, although enough may be collected from a stab in the lobe of the ear or in the thunb. One or 2 c.c. of blood are placed in a dry Wassermann tube. In this tube the serum separates from the clot either by standing or by centrifuging. In another

tube containing 1 c.c. of 2 per cent. sodium citrate[1] are placed 3 or 4 drops of blood. The suspension of corpuscles in this citrated plasma is used in the test without washing. On a cover-slip are placed 2 loopfuls of serum of the known group and 1 loopful of the corpuscle suspension of the unknown. A hanging-drop preparation is made. On another cover-slip are placed 2

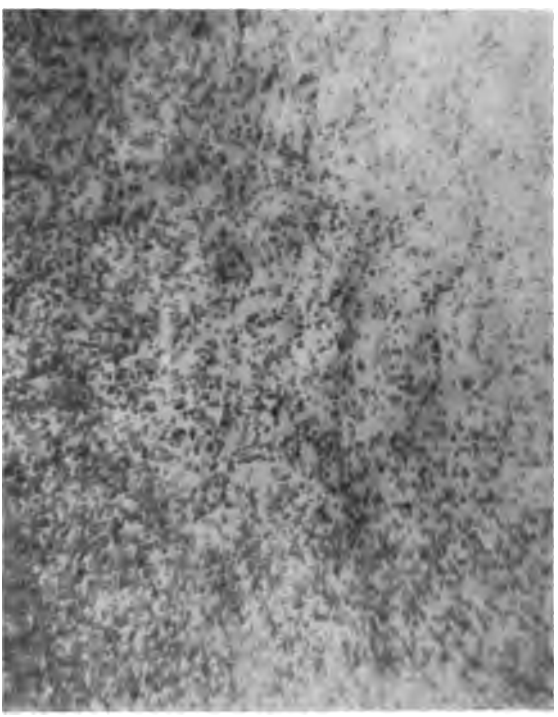


Fig. 164.—Microphotograph showing no agglutination of corpuscles.

loopfuls of the unknown serum and 1 loopful of the known corpuscle suspension and a second hanging-drop preparation is made. The slides are examined within a minute or two for evidence of agglutination. By holding the cover-slip securely on the slide the preparation may be rotated in such a manner

[1] Our sodium citrate solution is made 2 per cent. in 0.9 per cent. sodium chlorid solution (normal saline).

as to bring the serum and corpuscles well together. If agglutinins are present, clumping will begin almost immediately. The evidence of this may be seen with the naked eye. Figures 164 and 165 illustrate plainly the appearance of the blood when there is no agglutination and the characteristic clumping of corpuscles when agglutination is present.

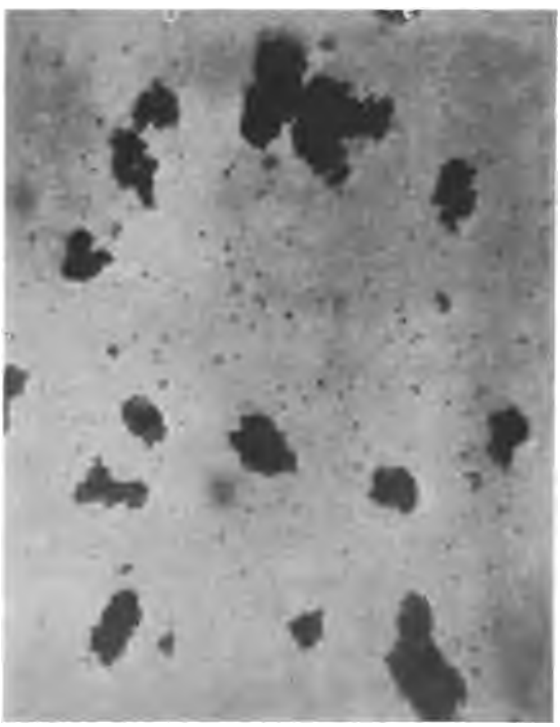


Fig. 165.—Microphotograph showing agglutination of corpuscles.

Reference to the diagram will make clear the determination of the group of the unknown with reference to the phenomenon of agglutination, or the absence of this reaction in relation to the known serum and known corpuscle suspension. If possible, it is preferable to use Group III blood in testing up unknowns, as there are so few persons in this group that it is but seldom that there is no agglutination on either slide. If the Group III

serum agglutinates the unknown corpuscles it is evident from the diagram that the unknown must be in either Group I or Group II, but which of these two groups the unknown is in cannot be determined until the action of the unknown serum on the Group III corpuscles is noted. If there is also agglutination of the Group III corpuscles by the unknown serum the unknown blood is in Group II, the reciprocal to Group III. That is, both hanging-drop preparations present sharp agglutinations when we are dealing with reciprocal groups. If the unknown serum does not agglutinate the Group III corpuscles when the unknown corpuscles are agglutinated by the Group III serum, the unknown blood is in Group I. On the other hand, if the Group III serum does not agglutinate the unknown corpuscles, the position of the unknown is on the right-hand side of the diagram and is in either Group III or Group IV. Group III blood is diagnosed by the fact that there is no agglutination of the Group III corpuscles by the unknown serum when there is no agglutination of the unknown corpuscles by the Group III serum. That the unknown blood is in Group III, the same group as the test blood, can be further proved by finding agglutination in both preparations when Group II blood instead of Group III is used for testing. Group IV blood is always diagnosed by the fact that the known corpuscles are agglutinated by the unknown serum, while the unknown corpuscles are not agglutinated by the known serum. This picture is the same whether Group III or Group II blood is used as the known test blood. This test may be carried out in from ten to fifteen minutes by using the centrifuge to obtain clear serum. The practical application of this method is as follows:

The group of the patient is determined. If volunteer donors are to be used their blood should be grouped and one selected who is in the same group as the patient. If professional donors are to be used, who have previously been tested, the donor of the proper group is sent to the operating room at the time the transfusion is to be carried out. The same technic may be employed when a surgeon has only an occasional transfusion, by directly testing the recipient's serum with the pro-

spective donor's corpuscles, even though blood of a known group is not at hand. This may be quickly carried out by using two loopfuls of the recipient's serum with one loopful of the donor's corpuscles. If there is no agglutination, the transfusion may be performed even though the donor's serum should agglutinate the patient's corpuscles, as the real danger in transfusion arising from incompatibility of donors lies solely in the action of the recipient's serum on the donor's corpuscles. Referring again to Diagram 1, it may be determined readily whether or not a donor of a certain group may be used for a patient of a different group, keeping in mind the rule that the recipient's serum must contain no agglutinin for the donor's corpuscles. It is evident, then, that Group I patients may have donors of any group, since there is no agglutinin in their blood. Group II patients may have donors of their own group or they may have also Group IV donors, as the corpuscles of either Group II or Group IV will not be agglutinated by Group II serum. In like manner, Group III patients may have either Group III or Group IV donors, while a Group IV patient must always have a donor of Group IV only. It is also evident that persons of Group IV are rightly called universal donors, as the corpuscles of this group are not agglutinated by the serum of any group, and it has been proved by practice that donors of this group may be used with impunity for persons in groups other than their own. In case of an emergency transfusion it is our custom always to send Group IV donors if there is not time to determine the group of the patient.

The Moss Method.—Another microscopic method much in vogue for grouping unknown persons is that devised by Moss. The technic is quite similar to the Brem method except that serums of Group II and Group III are used for testing the group of unknowns. It is necessary to obtain only a corpuscle suspension of the unknown blood and to make hanging-drop preparations with both Group II and Group III serum. Figure 166 illustrates the reaction that occurs between the unknown corpuscles and the known serums in each of the four groups. If the unknown is in Group I, there will be agglutina-

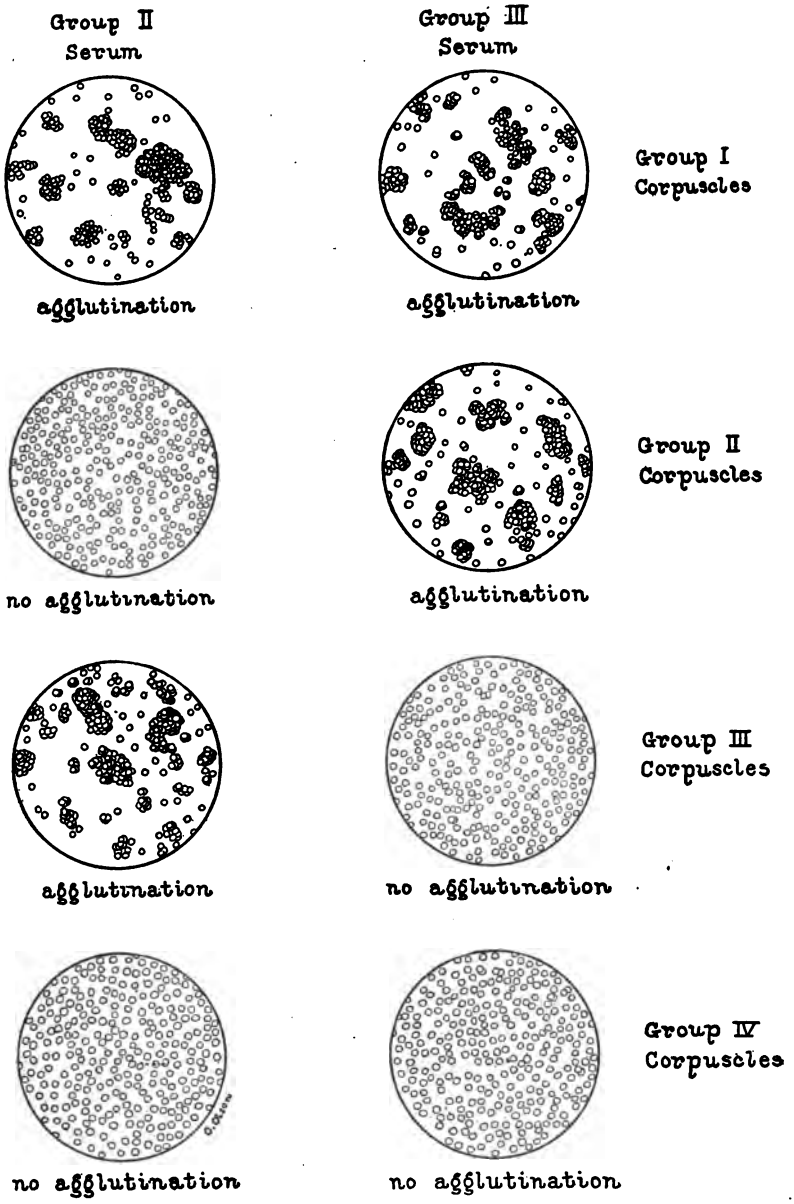


Fig. 166.—Appearance of hanigng-drop preparations of corpuscle suspensions of four different groups (Moss classification) used to dissolve Group II and Group III serum dried on cover-slips.

tion on both slides. Group II corpuscles will not be agglutinated by Group II serum, but will be agglutinated by Group III serum. Group III corpuscles will be agglutinated by Group II serum and not by Group III serum, while Group IV corpuscles will not be agglutinated by either Group II or Group III serum. The chief advantage in the Moss method is that Group II or Group III serums may be preserved in the ice-box for a considerable length of time, while the corpuscle suspension necessary for the Brem method will last but a few days. On the other hand, when fresh blood is obtained the Brem method gives a more clear-cut picture, especially in determining Group IV blood. By the Moss method Group IV is determined by the absence of agglutination on both slides. By the Brem method Group IV blood is quickly determined by the presence of agglutination of the known corpuscle suspension by the unknown serum.

I have previously reported a method for preserving serums of known groups to be used by the Moss method in laboratories desiring to start grouping tests in which no blood of a known group is at hand.[14] Serums of Group II and Group III are dried on cover-slips; the quantity is very small and one or two loopfuls of unknown corpuscle suspension will quickly redissolve the dried serum. It has been found that the agglutinins are not affected by drying and may be preserved thus for several weeks. When redissolved in the citrated plasma of the unknown corpuscle suspension, they readily act in their characteristic manner, and the unknown blood may be grouped according to the Moss method. It was also suggested that this method could be employed for sending blood to laboratories for grouping. On each of several clean cover-slips two loopfuls of the unknown serum should be placed and allowed to dry in the air. The group of the unknown serum may then be determined by noting the action both with Group II and Group III corpuscle suspension, simply reversing the usual Moss technic.

Since the publication of this method cover-slips have been sent to hundreds of laboratories. From many of these I have had very satisfactory reports; few complaints have been re-

ceived. There are doubtless some difficulties, however, in the use of serum dried on cover-slips for determining unknown groups. I am not advocating their use as a routine procedure, but merely claim for it advantage in the transportation of serum of known group to persons at a distance who desire to start the group method of selecting donors. If blood of Group II or Group III is found, tests may then be carried on by either the Brem or the original Moss method. One of the chief objections to the preservation of agglutinins by desiccation is that the preparation must be fresh. This has recently been brought out by Karsner and Koeckert. Their experiments were chiefly of interest in that dried serum after several weeks apparently acquired agglutinating properties of a non-specific nature. Even Group IV corpuscles were agglutinated by such serums when brought into solution. It has not been called to our attention that our cover-slip method has presented this difficulty in practice, although, to be sure, we have usually used only recently dried serums, and probably this is a necessary precaution.

Recently we have attempted further to improve the method of preservation of agglutinins in serums of known groups by a method of complete dehydration. The technic for this process was described by Burrows and Cohn, and consists, briefly, in exhausting the air in a distilling flask by means of a heavy suction-pump and allowing the serum to enter drop by drop into the partial vacuum through a drop funnel. The flask is heated during the process to about 50° C. in a water-bath. Beads should be placed in the flask to assist in removing the dried serum from the walls of the flask. A drop of serum when it enters the vacuum is immediately dehydrated and a fine powder collects which may be removed and kept indefinitely in a sealed glass tube. We have found that this powder will again go into solution as soon as it is mixed with normal salt solution, and that such dehydrated serum, when again in a fluid state, retains all the properties of the fresh serum as regards the presence of agglutinins.[1] There are, undoubtedly, many interesting investi-

[1] How soon non-specific agglutinating bodies, as referred to by Karsner, would develop in serum so desiccated cannot be definitely stated at this time.

gations that may be carried on by some method such as this with regard to the properties of antibodies. There may be very little practical value in the method as just described. However, I believe that serums of known groups could be shipped to the Orient or could be preserved for many months by complete dehydration, and that this method might be preferable to the attempt to use sealed ampules of fresh serum.

Many questions arise in connection with the phenomenon of iso-agglutination and the practical application of the laws of the selection of the donor for transfusion. Iso-agglutination is supposed to follow mendelian law. These iso-agglutinins are apparently true characteristics that are passed from parent to offspring according to the same laws as other inherited characteristics. If both parents are in the same group, the offspring would most likely be in the same group. If the parents are in different groups, the offspring may be in either group, or might possibly be in neither group, as it is conceivable that a child may get his group from a grandparent rather than from his father or mother, or that a new group might be formed by the combination of two different groups. We have seen a Group IV child with a Group II father and a Group III mother. Did this child get his Group IV characteristics by combining Group II and Group III characteristics, or did he inherit his group from a Group IV grandparent?

Another question that is often asked is with regard to the effect of transfusion on the person's group. It is not conceivable that a donor may be affected in any way by bleeding, nor does it seem at all likely that a patient's group is affected in any way by transfusion. There have been a few instances of apparent change of group after one or two transfusions, but I believe that it is more plausible to think that there was some error in the first determination of the person's group rather than to think that the introduction of blood of a compatible type has developed new agglutinins in the patient's serum, placing him in a different group. For instance, if a Group II patient were transfused with Group II corpuscles, in order to change his group he must acquire agglutinins for Group II corpuscles, thus placing him in

Group IV. At the same time the patient's own corpuscles would either be entirely agglutinated by the new agglutinin formed or they would simultaneously have to acquire an immunity against the new agglutinin. In this connection I might mention the fact that it is believed that the phenomenon of agglutination does not depend entirely on the presence of some substance in the serum, but that we may be justified in discussing the agglutinability of the corpuscles of the various groups. Our attention is often called to the fact that a fresh suspension of corpuscles agglutinates much more rapidly with the given serum than does a suspension that has stood for several days and is nearing the point of beginning autolysis.

It was stated some time ago by Cherry and Langrock that in transfusions in the newborn the blood of the mother could always be used with impunity. The series of transfusions reported, however, was far too small to make this rule absolute, and the subject should be investigated further. If it is true, interesting speculations may arise. Are the newborn in no group? Or, in the first few weeks are they in the same group as the mother? Such points will probably soon be cleared up by investigators working in children's hospitals.

THE TECHNIC OF TRANSFUSION

The subject of transfusion has been very thoroughly studied at the Mayo Clinic by Pemberton. His report published in 1918 contains a full bibliography of the literature of transfusion. The various methods that have been advocated from time to time have been given trial at the clinic by different surgeons. Several years ago the direct vessel-to-vessel method was employed. Of the indirect methods there have been a few transfusions undertaken by the use of large syringes. This method is rapid, provided that the surgeon is dexterous, has a sufficient equipment, and good assistants. It is necessary to work rapidly so that there will be not the slightest change in the blood at any time in the operation. Another method much in vogue is the use of a paraffined tube, which is thus prepared to prevent clotting. Its chief claim for attention lies in the fact that

Fig. 167.

whole blood, unaltered in any way, is transferred in measured quantities from the donor to the recipient.

The method that has been used by Pemberton and his coworkers for a number of years and is still employed has proved to be very satisfactory in a large series of transfusions. This is usually referred to as "Lewisohn's method"; it depends for its simplicity on the use of 2 per cent. sodium citrate to decalcify the donor's blood so that coagulation is prevented. The technic, quoted from Pemberton's recent article, is as follows:

"The blood is received in a sterile graduated glass jar containing 20 c.c. of a 2 per cent. sterile solution of sodium citrate at the bottom. While the blood is running it is well mixed with the citrate solution by means of a glass rod. The flow of the blood should be in a steady, continuous stream, and when there occurs slowing of the stream, as is often observed with a sudden drop in venous pressure, due either to syncope or the too snugly applied tourniquet, the needle should be immediately withdrawn and a clean one inserted. If the blood is allowed to flow in an impeded stream, there will be clotting of the whole or part of the blood collected because of the incipient coagulative changes which have taken place in transit from the vessel to the citrate solution. After the blood has reached the 250 c.c. mark another 30 c.c. of the citrate solution is added and the blood is permitted to flow until there are 500 c.c. of the mixture. If more blood is desired, a sufficient amount of citrate solution is added to maintain this ratio of 0.24 per cent. The blood may be carried to the recipient's room or the recipient may be brought into the operating room. The needle is then introduced into the recipient's vein, after the manner above described, and attached by rubber tubing to a glass irrigating flask, the tubing and the bottom of the flask having been previously filled with saline solution. The citrated blood is then transferred into the flask

Fig. 167.—*A*, Cross-section of vein transfixed in its upper segment to skin by a straight intestinal needle. *B*, Introducing Kaliski cannula into the cephalic vein of the donor. The vein is steadied and prevented from rolling from under the cannula by means of slight traction exerted upon the transfixing needle. *C*, Cannula introduced in vein of recipient. (Pemberton.)

and permitted to flow into the vein of the recipient. It is advisable to have the blood run slowly in order to guard against suddenly overloading the right side of the heart, and in order to watch for any untoward effects upon the patient."

One of the chief advantages of this method is that since the danger of coagulation has been removed there is no necessity for haste in the operation. It is usually not necessary to cut down on the donor's or patient's veins in order to withdraw or introduce the blood. Figure 167 indicates a simple method employed by Pemberton for immobilizing the vein for venipuncture, using a cambric needle.

In concluding I would again state that when transfusion is indicated, no matter what operative procedure is the method of choice, the chief point of consideration is the selection of a donor, who, above all else, must be of the group whose corpuscles are compatible with the recipient's serum.

BIBLIOGRAPHY

1. Ashby, Winifred: The Determination of the Length of Life of Transfused Blood-corpuscles in Man, Jour. Exper. Med., xxix, 267–281, March 1, 1919.
2. Burrows, G. H., and Cohn, E. J.: A Quantitative Study of the Evaporation of Blood-serum, Jour. Biol. Chem., xxxvi, 587–590, December, 1918.
3. Cherry, T. H., and Langrock, E. G.: The Relation of Hemolysis in the Transfusion of Babies with the Mothers as Donors, Jour. Amer. Med. Assoc., lxvi, 626–627, February, 1916.
4. Karsner, H. T., and Koeckert, H. L.: The Influence of Desiccation on Human Normal Isohemagglutinins. Jour. Amer. Med. Assoc., xiii, 1207–1210, October 18, 1919.
5. Landsteiner, K.: Zur Kenntnis der antifermentativen, lytischen und agglutinierenden Wirkungen des Blutserums unter der Lymphe. Centralb. f. Bakteriol., xxvii, 357–362, March, 1900.
6. Landsteiner, K.: Ueber Agglutinationserscheinungen normalen menschlichen Blutes, Wien. klin. Wchnschr., xiv, 1132–1134, November, 1901.
7. Moss, W. L.: A Simple Method for the Indirect Transfusion of Blood, Jour. Amer. Med. Assoc., cxlvii, 698–703, May, 1914.
8. Moss, W. L.: Isoagglutinins and Isohemolysis, Johns Hopkins Hosp. Bull., xxi, 63–70, March, 1910.
9. Ottenberg, R., and Libman, E.: Blood Transfusion: Indications; Results; General Management, Amer. Jour. Med. Sci., cl, 36–69, July, 1915.

10. Pemberton, J. de J.: Blood Transfusion, Surg., Gynec., and Obst., xxviii, 262–276, March, 1919.
11. Pemberton, J. de J.: Practical Considerations of the Dangers Associated with Blood Transfusion. Paper presented before the Des Moines Valley Med. Assoc., June 26, 1919, Ottumwa, Iowa.
12. Sanford, A. H.: Isoagglutination Groups. A Diagram Showing their Interrelation, Jour. Amer. Med. Assoc., lxvii, 808, 809, September 9, 1916.
13. Sanford, A. H.: Selection of the Donor for Transfusion, Jour.-Lancet, xxxvii, 698–701, November 1, 1917.
14. Sanford, A. H.: A Modification of the Moss Method of Determining Isohemagglutination Groups, Jour. Amer Med. Assoc., lxx, 1221, April 27, 1918.

CLINIC OF DR. JOHN H. STOKES

1. **A Case of Early Lepra.**
2. **Solitary Cutaneous Nodular Recurrences as Aids in the Diagnosis of Obscure Visceral Syphilis.**
3. **Three Cases Illustrating the Diagnosis and Treatment of Syphilitic Involvement of the Nervous System.**
4. **The Etiologic Analysis of a Chronic Urticaria Following Influenza Vaccination.**
5. **Interstitial Keratitis in Heredosyphilis Following Influenza, with Comment on Treatment.**
6. **The Protection of the Kidney in Intensive Antisyphilitic Treatment, with Special Reference to the Influence of Dental Focal Infections.**

CASE I (285264)

I WANT to open my clinic by presenting to you in a retrospect, illustrated by the patient before you, 4 cases which have passed through this clinic since 1916. Mike Saras came to the clinic to secure relief from pain in the legs, a lame back, and a sore throat of nearly one year's duration. The resemblance of these complaints to those frequently made by syphilitics is apparent enough. It needed only three successive positive Wassermann reactions to convince a former medical attendant that arsphenamine treatment was in order. Seven intravenous injections of the drug failed to relieve the symptoms. A year before the patient appeared at the clinic a nodule had been excised from the right hand and he had been told that he had a mixed-cell sarcoma.

On objective examination, from the standpoint of the internist, this patient presented somewhat variegated findings, summarized as follows:

Moderate pyorrhea.

Tonsils small and septic.

Atrophic rhinitis.

Testicles enlarged and hard.

Incomplete right direct inguinal hernia.

A well-marked general adenitis with glands the size of a robin's egg in the left axilla (side from which the supposed sarcomatous nodule was removed).

Radiogram shows what appears to be a tuberculosis of the left apex.

Spastic stiffness of gait apparently due to lumbar pain.

Cardiovascular and renal systems negative.

Inevitably the next step in the examination of such a case might seem to be the removal of an axillary gland to settle the question of metastatic malignancy suggested by the nodule on the hand as against tuberculosis suggested by the *x*-ray findings in the chest. Pathologic examinations of the excised glands seemed to establish the diagnosis of a glandular tuberculosis. The glands exhibited an epithelioid hyperplasia with caseation necrosis and giant-cell formation. The epithelioid hyperplasia seemed rather diffuse for a typical tuberculosis, but this point alone was hardly enough to force a modification of the pathologic diagnosis.

At this point in his examination it was noticed that the patient presented scattered papules of a pinkish or purplish color over the forearms. The emphasis this department is in the habit of placing on association of certain cutaneous manifestations (tuberculids) with tuberculous glands, and the favorable response of such cases to arsphenamine, led to the referring of the patient to us.

In reviewing the dermatologic examination I would like to give you first of all the impression spoken of in slang terms as the "hunch" or instinctive reaction aroused by the facies and general make-up of this patient (Fig. 168). He is a foreigner, evidently a Greek. His gait has a distinctly shambling quality, as of one who, though entirely oriented as regards his sense of motion and position, does not quite feel the substance on which he walks. His hands are a little large, a little blue, a little pudgy. The face exhibits a pigmentation more olive than

even his race would justify. The eyebrows beetle slightly; there is a distinct loss of hair on the outer halves. His voice is husky, he snuffles persistently. On stripping him we find, in addition to the rather nondescript macules and papules of his eruption, the scars of large destructive lesions over the knees. The patient explains these by saying that when he had

Fig. 168.—Facies of early lepra. Note the peering, slightly anxious expression, the thinning of the hair and the outer halves of the eyebrows and the scattered papules about the forehead. The left cheek contains a large, palpable, but not visible tumor-like mass. There is a cicatricial stenosis of the larynx. Wassermann positive.

rheumatism he put hot bricks to his knees and burned them before he realized what had happened.

The search for firm fleshy nodules in the face, which should always be made in the presence of such findings as these, is without result in this case. Diffuse violacious, slightly infiltrated plaques may be recognized, however, by a transverse light, in the integument over the buttocks, and the papules on the arms

and trunk have the distinct firm induration which suggests granulomatous infiltration.

Three more moves establish the diagnosis. The ulnar nerve, palpated as it crosses the olecranon process of the ulna, is hard, somewhat nodular, practically painless, and as large as a small lead pencil. On instructing the patient to close his eyes a pin test quickly establishes the presence of irregular islands of almost total anesthesia on the extremities. It may be accepted as axiomatic that to burn the knees of a normal person not under anesthesia cannot be done without a struggle. The average man is as kind to his knees and shins as a bear to his nose. The third move clinches a diagnosis already all but established. The patient's nasal secretions contain many leukocytes within whose cytoplasm may be found the typical acid-fast *Bacillus leprœ*.

Two points need primary emphasis here. The favorite mask of lepra is under the guise of lues. Lepers are not infrequently Wassermann positive on the blood, whether from coincident syphilis or some peculiarity of the disease it is difficult to say. Two of the four lepers in our group have had positive Wassermann reactions in the clinic and three of them had been treated for syphilis. The potential resemblances to tuberculosis are less conspicuous. In this case the pathology of the excised gland inevitably suggested tuberculosis. Unfortunately, the fixation method used interfered with proper staining for acid-fast bacilli. That the diagnosis in this case was ultimately made by a dermatologist does not mean that the diagnosis of early lepra is not a problem in otolaryngology, neurology, and internal medicine. While lepra is by no means a common disease, there can be no question that it frequently passes unsuspected through offices and clinics. Recognition of late lepra calls for no particular skill. A classical leonine facies, extensive ulceration, advanced syringomyelic changes, and involvement of the bones usually suggest the diagnosis at once. The recognition of early lepra, on the other hand, depends on less tangible clues. It is an urgent duty to recognize early lepra because of the improved therapeutic outlook for the disease made possible by recent modifications of chaulmoogra oil therapy. Its early rec-

ognition may be facilitated by a certain alert suspiciousness of mind and a "hunch" or intuitive impression, the visual elements of which I have tried to define in picturing this case. Shambling gait and pudgy syringomyelic hands, the slight thickening of the brows even without palpable nodule formation, the thinning of the outer half of the eyebrows, changes in the larynx that comport with late gummatous rather than secondary syphilis, a palpably enlarged, insensitive ulnar nerve, islands of anesthesia that may be detected by five minutes' work with a pin-point, the residua of burns, and a nondescript papular eruption, demand a nasal smear. In every one of the 6 lepers seen in the clinic since 1913 the nasal smear has established the diagnosis through the finding of the typical acid-fast intracellular organism. A wider application of this simple diagnostic test would prove illuminating in more than one obscure pseudoluetic and pseudotuberculous picture.

CASE II (246034)

I shall present this patient to you exactly as she came to me. She accompanied her husband to the clinic to have him undergo examination for supposed nervous prostration. While here it occurred to her that she might as well find out why she was occasionally more short of breath than her weight seemed to justify. Her very obvious good health did not stimulate a particularly searching examination, and before the study of her case was many hours old she was referred to the dermatologist for an opinion as to the treatment of "eczema" on her left arm. In spite of the fact that it was represented to her that the unvarying custom of the dermatologist demanded a complete examination of the body surface, she declined to do more than expose her left forearm, saying that that was all there was to it. We looked at the forearm, and encountered one of the most distinctive contributions of the dermatologist to general diagnosis.

This patient presents scattered over the flexor aspect of the left forearm from the elbow to the wrist about a dozen faintly visible atrophic patches of various sizes. The smallest of the original lesions were split-pea-sized papules of a pinkish to

fawn color and of a peculiar "deep" or infiltrated feel (Fig. 169). The most striking lesion was the semicircular crescentic ridge with the convexity upward which lies on the outer anterior aspect of the forearm at the site of the crescentic scar-like atrophy just below the flexure of the elbow. I want particularly to direct your attention to the original characteristics of this lesion, now no longer apparent; to its deep palpable induration, suggesting that it, like an iceberg, was nine-tenths below and one-tenth above the surface; to its indolently inflammatory character; to the slightly translucent fawn to brown-red sheen; and to the

Fig. 169.—The crescentic and papular, infiltrated lesions of Case II. A solitary cutaneous nodular syphilitic recurrence. Blood Wassermann repeatedly negative; spinal fluid negative, but with beginning aortitis.

faint suggestion of crinkling (atrophy) at the tips and along the convexity of the crescent. This lesion in itself constituted a diagnosis, and was properly a foundation for at least the gravest suspicions. Allow me to impress upon you the fact that there is no more serious error possible in dermatologic diagnosis than to make light of an indurated, arciform, or crescentic lesion. Indurated crescentic lesions, ulcerative or non-ulcerative, are, figuratively speaking, the signet rings of lues. If they present evidence of peripheral extension with cigarette paper atrophy due to the destruction of the elastica of the cutis in their wake, they are doubly suspicious. It is at least permissible to suspect

them of being granulomatous. From the familiar diagnostic resort of inexperience, "ring worm," such lesions are to be distinguished by the absence of peripheral vesiculation and pustulation. Erythematous lupus on the face occasionally mimics these lesions, although it is usually more definitely annular or ring-shaped in configuration and symmetric in distribution. Lupus erythematosus, moreover, is always accompanied by the basic structural changes of patulous follicles, follicular epithelial plugging, in addition to the atrophy.

Without fatiguing you too much with the minutiæ of differential diagnosis, for the recognition of these lesions is to some extent a matter of instinct, I want to recount to you the subsequent history of this case.

In her preliminary examination the patient was described as a woman of robust health, slightly overweight, with a blood-pressure of 146/78, definite pyorrhea, many filled and crowned teeth, normal urine, and an accentuated cardiac second sound. She had been married twenty-three years, had no children, and had sustained two miscarriages, one of them induced. The aggregate of her complaints gave a confused neurasthenic impression—throbbing at the back of the neck, a sense of tightness in the chest on exertion sometimes amounting almost to a pain, a sense of constriction in the throat, slight headache, slight shortness of breath, and a feeling of cold and numbness in the arms. The Wassermann on the blood was negative. We will now excuse the patient from the room.

The dermatologist ungraciously insisted that this patient has lues in bold defiance of the negative Wassermann. He insisted upon a combined provocative Wassermann and therapeutic test. Seven consecutive Wassermanns following a small injection of arsphenamine were as negative as the first; but the behavior of the lesion gave the clue to the situation. On the eighth day following the small injection of 3 dg. of arsphenamine the "eczema" of the forearm, including the crescentic lesion previously discussed, had practically disappeared.

Following the very prompt therapeutic effect on the cutaneous lesions, the patient was asked to enlighten me on one or two de-

tails of her previous life on which no history had been obtained. When she was told that there was very little doubt that syphilis was the condition underlying both the skin trouble and the trouble in the chest she admitted antemarital exposure at the age of eighteen. An internist was again called in consultation, and, whether from the lighting up process induced by the previous arsphenamine injection or because suspicion was now definitely focused on a particular point, a low reverberant systolic murmur, not transmitted, could now be heard over the aortic area. The internist comments: "This, with a history of retrosternal pain, makes aortitis quite definite." Seven months later a systolic murmur transmitted to the carotids was easily recognized. A markedly retarded reaction of the pupils to light was noted, but the examination of the spinal fluid yielded negative results.

This case illustrates the diagnostic value of a solitary late cutaneous recurrence in the skin as a clue to the recognition of obscure syphilis. Palmar syphilids of this type have not infrequently been Wassermann negative by a conservative technic in our experience, and the diagnosis has had to be established by other means. Occasionally the negative Wassermann can be reactivated by a provocative procedure. The so-called Jarish-Herxheimer reaction in the lesion, akin to the focal flare-up of a tuberculous lesion on the injection of tuberculin, is frequently a material diagnostic aid. A warning should be given against protracted therapeutic tests with arsphenamine in doubtful skin lesions, since a variety of non-specific dermatoses may show a favorable response to the prolonged administration of an arsenical compound. If a lesion of this type has not flared up and then almost vanished within eight or nine days after a 3-dg. dose of arsphenamine, I begin to suspect the lesion of being non-specific.

Two things the internist can profitably learn from the dermatologist: first, never to underestimate induration, atrophy, and scarring associated with a cutaneous lesion, and second, to feel a sudden wave of suspicion sweep over him at the sight of an arciform or crescentic configuration. In these days of

Wassermann rule-of-thumb clinicians it is at times difficult to persuade an examiner that the clinical syphilology of Fournier still dominates the Bordet-Gengou phenomenon.

CASE III (263159)

I am going to present to you in rapid succession 3 patients, placing on the blackboard behind them as they enter the results of the examination of their spinal fluids to illustrate the discussion of their cases when they leave.

This patient, who is masked, presented herself at the clinic with a diagnosis of carcinoma. The lesion at the urinary meatus had, however, developed with suspicious rapidity for a carcinoma. It was at the time of her first examination approximately of four weeks' duration. It consisted of a firm erosion apparently on the lower lip of the meatus, evidently, to judge from palpation, extending upward along the canal. The exposed portion of the erosion was covered with a glairey discharge, and presented a fairly clean base and a dark hemorrhagic border. The *Spirochæta pallida* was identified in large numbers in the discharge. There was a marked palpable, bilateral inguinal adenopathy, but no signs of mucous lesions about the mouth or genitalia, nor was there anything to suggest a secondary eruption. The blood Wassermann, however, was positive, indicating that the infection had generalized.

Should the Wassermann test have preceded the dark-field examination in this case? In general, no. Lesions of this type can often be identified as syphilitic by dark-field as long as two weeks before the Wassermann becomes positive.

In a lesion of this duration, with a positive Wassermann, why does the patient not show secondary manifestations? In our experience the secondary eruption may be absent, overlooked, or ignored in as high as 65 per cent. of patients with obscure lues.

This patient was placed at once on intensive arsphenamine and mercurial therapy. Within nine days she received 15 dg. of arsphenamine. To the third injection she responded unfavorably, with a threatened exfoliative dermatitis. By a combination of thorough alkalinization and the colloid bath

the skin was restored to normal, daily intramuscular injections of mercury succinimid were begun, and the arsphenamine resumed. Her tolerance was so far improved that after fifty-two days of this therapy all gross evidence of her infection had disappeared. Her Wassermann had been negative since the third injection of arsphenamine. On her insistence, we prepared to discharge her to the care of her home physician, with instructions that her mercurialization should be continued and that her arsphenamine should be resumed after a rest period of one month. It is an established practice of this service, however, that no primary or secondary stage infection, regardless of the blood Wassermann, shall be placed on a rest period without an examination of the spinal fluid. Such an examination performed on this patient disclosed a Wassermann negative with 0.3 and 0.4 c.c., Nonne positive, 102 small lymphocytes, and a negative gold sol test. A lymphocytosis of this type in the presence of a luetic infection can only mean a marked meningeal involvement.

Certain important considerations hinge on this finding:

1. This patient's infection had, in spite of the absence of secondaries, involved the nervous system. Involvement of the central nervous system in what seems to be the primary or localized stage of syphilitic infection is by no means uncommon.

2. This involvement had occurred in spite of intensive modern treatment and illustrates how impossible it is to predict the reaction of the soil on which the *Spirochæta pallida* is implanted. A neuroreceptive type of patient may, for unknown reasons, develop the most alarming of localizations where an unreceptive individual is unaffected. Had this patient been discharged from observation, as is so frequently the practice, without an examination of her spinal fluid, and on the basis of an easily obtained negative Wassermann in the supposed primary stage of infection, she would have been a promising candidate for the unfortunate type of accident called a neurorecurrence.

Is it reasonable to assume that an inadequate therapy is responsible for the condition of the nervous system? The same therapy applied systematically to a large number of cases has yielded, on the whole, highly satisfactory results. It is not im-

possible, however, that this patient is infected with an organism presenting a high resistance to arsenic therapy.

Is there no other means than a spinal puncture of recognizing a situation of this sort in time to prevent unfortunate complications? There is not. An extensive degree of involvement of the nervous system in early syphilis may be present in the complete absence of neurologic signs and objective symptoms.

This patient was placed at once on massive therapy. Since we knew from her previous cutaneous reactions that she had only a limited tolerance of arsphenamine, a resort to an entirely different method was necessary. She was placed at once on double the average adult dose of mercurial ointment, by inunc-

Table 1. CASE 263159

Date	Arseno-benol	Mercury Pluvin.	Inunctions	Potassium iodid	Sodium iodid	Blood Wassermann	Cerebro-spinal fluid Wassermann	Nonne	Cells	Lange
March 13, 1919 to May 8, 1919	VII		4 gms. XII			3/13/19 +++				
April 7, 1919 to May 10, 1919		17				4/12/19 neg.				
						4/24/19 neg.				
May 20, 1919 to June 21, 1919			8 gms. XXV	Potass. iod. M. XX to G t.i.d.	30-100 c.c. daily 1395 c.c. Intravenous		5/15/19 neg. .3 & .4 c.c.	pos.	102	0,0,0,0,0,0,0,0,0,0
							6/6/19 neg. .3 & .4 c.c.	neg.	16	0,0,0,0,0,0,0,0,0,0
							6/24/19 neg. .3 & .4 c.c.	neg.	4	
						6/30/19 neg.				

Fig. 170.—Treatment chart of Case III. This patient was to have been discharged for home treatment when a routine spinal puncture May 15, 1919, showed a high grade of central nervous system involvement. Improvement under therapy is shown by the subsequent examination.

tion, and in thirty-one days received intravenously 6725 gr. of sodium iodid (an average of 217 gr. a day) combined with 450 gr. a day by mouth. The response of her nervous system to this therapy is indicated in Fig. 170. Thirty-nine days after our discovery of the meningeal involvement the patient's spinal fluid was normal. While it is conceivable that a spontaneous resolution might have occurred, it seems in the highest degree improbable.

In cases of this type some authorities vigorously commend the intraspinal use of arsphenamine. I have not, personally, been able to escape the feeling that to depend on intraspinal therapy in such cases is to lose sight of the whole in contemplation of the

part. Syphilis at this stage of the individual infection, regardless of Wassermann and physical findings, involves the entire body. The intensity of the average Swift-Ellis treatment, so far as the body as a whole is concerned, is low. It is primarily a localizing method. A large proportion of central nervous system involvement in early syphilis will yield to intensive general methods, to the advantage of the patient as a whole. Such methods should not be lightly discarded, nor should we be driven in a panic to intraspinal therapy on the first sign of cerebrospinal involvement. When intensive general therapy fails in a properly controlled case there is still time to resort to the localizing measures of intraspinal treatment (Fig. 170).

CASE IV (224251)

This gentleman's condition on first examination was the result of a failure adequately to treat by standard methods and adequately to control the results in an infection of the same type as that of the preceding patient. Six months ago this patient developed a lesion on the lip which was misinterpreted and subjected to desultory local treatment. After the lesion had been present six weeks a secondary eruption appeared which was recognized, and the patient received three injections of arsphenamine and ten injections of mercury salicylate. The eruption and the primary lesion promptly disappeared. After the discontinuance of treatment (whether on the patient's option or his physician's does not appear) he received a jolt while riding, and almost immediately thereafter developed nausea, vomiting, severe headache, and rapidly failing vision.

General clinical examination disclosed a somewhat anemic man, slightly underweight, with a negative blood Wassermann, and a severe neuroretinitis recognized by ophthalmoscopic examination. Examination of the spinal fluid disclosed a positive Wassermann on four concentrations, negative Nonne, and 106 small lymphocytes. In a series of seven blood Wassermanns following the first arsphenamine injection two reports were strongly positive (provocative effect?).

This is a classical example of the so-called neurorecidive

Has arsphenamine received an adequate try-out in this patient or has its abandonment been forced by a toxic reaction? Certainly not. Three injections in a fully developed secondary case can only be construed as the mere beginning of systematic treatment. To a case of this type it is permissible to apply the maxim, "The remedy for insufficient salvarsan is more salvarsan." The symptomatic response in this case was immediate and gratifying. Vision improved, the patient regained strength and weight, and returned to work, continuing his therapy by inunctions and arsphenamine. The second spinal fluid examination made four months after the first yielded a completely nega-

Table 2. CASE 284351

Date	Arsphenamine (Neosalvarsan)	Mercury Succinate	Inunctions	Potassium iodid	Sodium iodid	Blood Wassermann	Cerebrospinal fluid Wassermann	Nonne	Cell	Remarks
March 12, 1918 to April 19, 1918	VI	19		Taking KI. m.V- XXX t.i.d.	Provocative	3/12/18 neg. 3/13/18 neg. 3/14/18 +++ 3/15/18 neg. 3/16/18 +++ 3/19/18 neg. 3/20/18 neg. 4/13/18 neg.	3/18/18 ++++	neg.	106	Entered with violent headache, nausea, failing vision (neuroretinitis) Headaches gone Vision now normal
April 20, 1918 to June 20, 1918		40				7/13/18 neg.				Returned, gained 20 lbs.
July 13, 1918 to Aug. 31, 1918	VI	20		K.I.m. V-XXX t.i.d.		8/19/18 neg. 1/18/19 neg. 5/17/19 neg.	7/15/18 neg. 3 c.c.; 4 c.c.	pos.	5	Good condition Working steadily
June 14, 1919 to July 19, 1919	VI	rubs					6/30/19 neg. 3 c.c.; 4 c.c.	pos.	3	Doing well

Fig. 171.—Treatment chart of Case IV, a typical neurorecurrence, the result of inefficient early treatment. The first spinal fluid examination March 18, 1918, was taken when treatment in the clinic was begun. Note the satisfactory response under routine measures without the use of intraspinal therapy.

tive result, which was confirmed by a negative one year later. During this time the patient received eighteen arsphenamine injections, eighty inunctions, and nineteen injections of mercury succinimid intramuscularly. There has been no need to resort to intraspinal medication.

Is it invariably safe to institute arsphenamine therapy without mercurial preparation in patients exhibiting acute meningeal involvement? It is not. It is a safer plan in general to precede arsphenamine by a week of treatment with intramuscular injections of a soluble mercury salt.

Is the neuroretinitis a contraindication to the use of a supposed neurotropic drug such as arsphenamine? In our experience

it is not. The neurotropic properties of arsphenamine are more conspicuous in theory than in practice.

Was the jolt or jar which the patient received a predisposing cause of his neurorecurrence? In this case probably not. The influence of factors reducing general or local resistance of tissues to syphilitic changes is, however, very great. It is not uncommon in my experience to find examples of the onset of acute cerebrospinal symptoms in tabes, for example, dating from overstrain, from blows on the back, from falls, from heavy lifting, from industrial accidents, and from intercurrent infections.

Is it possible in early syphilis to have a negative blood Wassermann with positive findings on the cerebrospinal fluid? I believe that it is, and it is this belief which leads me to insist that no patient with a primary or secondary case shall be long under my care or discharged from my immediate observation, even when Wassermann negative, without a careful study of the spinal fluid (Fig. 171).

CASE V (227053)

Mr. R. came to the clinic with a history of primary lesion three and one-half years ago. He apparently had had no secondary eruption, but his treatment was begun at a time which would leave little doubt that his infection had generalized. He received in two years twenty-three injections of arsphenamine in courses of five injections each and mercury salicylate intramuscularly once a week, never less than twelve injections to the course, practically continuously during the time he was receiving his arsphenamine. Although the patient had no symptoms to complain of when he presented himself here, he was skeptical about his cure, although he had been assured by his physician that everything demanded by modern practice had been done and that he was well. A preliminary Wassermann test was negative. In a provocative series of seven tests, however, two strong positive and three weak positive reactions were obtained. A spinal fluid examination was then performed and a positive Wassermann, positive Nonne, and a cell count of 71 lymphocytes obtained, with a gold sol test of 4333320000. A neurologic examination was then requested, and although the neurologist

was advised as to the findings, practically no other objective evidence of involvement of the nervous system could be identified. The Achilles and patellar reflexes were slightly accentuated.

The patient was placed on intensive treatment with spinal drainage in amounts varying from 20 to 40 c.c. following each injection of arsphenamine. The successive fluid findings varied considerably, as shown in Fig. 172, but there was no evidence of rapid serologic improvement. The patient was discharged at the end of his first course of treatment to receive intraspinal injections by the Swift-Ellis method elsewhere.

Table 2. CASE 227063

Date	Arsphenamine (Ehrlich)	Mercury Bichloride	Bismuth Subsalicylate	Potassium Iodide	Sodium Iodide	Wassermann	Cerebrospinal fluid Wassermann	Mastic	Colloidal Gold	Lange	Spinal drainage	Remarks
April 3, 1918 to June 6, 1918	VI	21			Provocative	4/3/18 neg. 4/4/18 ++++ 4/5/18 + 4/6/18 wk.pos. 4/8/18 pos. 4/9/18 ++++ 4/10/18 neg.	4/9/18++++ 4/24/18++++ 5/4/18++++ neg..2 c.c. +++ .3,.4,.5c.c. neg..2 c.c. 5/14/18+++ .3 c.c. ++ .4 c.c. + .5 c.c. 5/24/18 neg.2 c.c. +++.3,.4,.5c.c. 5/24/18 neg.	pos. - neg. neg. neg.	71 - 26 13 26	4,2,2,2,2,2,0,0,0,0 - 1,2,2,2,2,0,0,0,0,0,0,0 0,0,0,0,0,0,0,0,0,0 4,4,4,3,3,3,3,2,0,0,	20 c.c. 30 c.c. 17 c.c.	3 yrs. intensive previous treatment Neurologic examination neg. No symptoms
						5/24/18 neg.	6/6/18 wk.pos.2..3c.c. +++ .4,.5 c.c.	neg.	56	1,1,1,1,0,0,0,0,0,0	24 c.c.	

Fig. 172.—Treatment chart of Case V, a patient who before his appearance in the clinic had received three years of standard, intensive intravenous and intramuscular therapy. Note the high grade of cerebral spinal involvement in a supposedly cured case and the comparatively slight response to six weeks of intensive therapy.

What does this third case teach us? First of all it teaches that there is the widest variation in the systemic response of different patients to so-called modern treatment. This patient had received what might in general be called modern treatment delivered by rule-of-thumb. At its termination he presents, instead of the expected cure, serologic findings highly suggestive of a general paresis. The paretic zone gold sol curve, while not conclusive evidence of this type of parenchymatous degeneration, cannot be lightly disregarded. A further trial of intensive therapy reinforced by spinal drainage failed to produce any sustained response. The failure of three years of a standardized routine procedure to cure this patient is the best imaginable il-

lustration of the folly of rash generalizations on the curability of syphilis. Whether this man has a predisposed nervous system, a neurotropic strain of infecting organism, or an infection that is both arsenic and mercury fast, if such exists, does not invalidate the practical maxim that the cure of syphilis, while possible, is not predicatable, and that any one of the three fac-

Table 4. CASE 216746

Dates	AB.	Hg.Succ.	Rubs	KI	Na.I	Bl.Wass.	CSF Wass.	Nonne	Cells	Lange	Sp.Dr.	T.S.
12/24/17-1/28/18	VI	3	18	0	0	+++ neg.	-	-	-	-	-	-
1/28/18-4/27/18	-	-	80	0	0	4/27/18 +	-	-	-	-	-	-
4/27/18-5/13/18	IV	-	-	-	-	5/13/18neg.	-	-	-	-	-	-
5/13/18-8/6/18	-	-	40	-	-	-	neg..3cc. .4cc.	neg.	61	-	-	-
8/23/18-10/16/18	V	30 to 9/16/18				neg.	neg..2cc. .4cc.	neg.	46	0001221000	-	-
10/16 - 11/1/19	-	-	12	-	-	neg.	+++ .3.4cc.	pos.	80	-	40cc.	-
11/1/19-11/20/19	-	-					+++ .3.4cc.	pos.	220	-	80cc.	
11/20/19-12/17/19	-	-	Double 28 X 2	Mouth 450 Rectum 150 14,000 gr.	50-100cc. daily 3,000	-	+++ .3.4cc. -	pos. -	293 -	- -	- -	- -
12/17/19-12/26/19	-	Treatment crisis and rest period				-	+++ .3.4 12/26/19	pos.	44	455431000	-	-
12/31/19-1/23/19	-	-	Double 22 X 2	Mouth 450 Rectum 450 900gr.daily 18,700	50-100cc. daily 1950 cc.	-	+++ .3.4 1/16/19	pos.	34	5433320000	-	-
1/23/19-2/4/19	-	Treatment crisis.		Nephritis.	Fischer's solution etc. Rest period prompt recovery (4 days)							
2/4/19 - 2/3/19	-	-	Double 24 X 2 (Potus)	Mouth 450 Rectum 450 daily 2700	50-100cc. daily 2250 cc.	-	neg..3cc. +.4cc. +++ .3.4cc.	pos. pos.	21 35	5554321C0 0011100000	- -	- -
2/3/19 -3/18/19 Kidney reacting throughout period but controlable			- (Potus	Mouth 450 Rectum 450 daily 13,500	100cc. daily to 3/13/19 1000 cc.	-	neg..2cc. .4cc. +.3cc. +.4	pos. pos.	9 5	1122211000 0000100000	- -	- -
3/18/19-3/22/19	-	Treatment crisis and rest period					-	-	-	-	-	-
3/22/19-4/8/19	-	-	-	Mouth 300-450 4,500 gr.	100 cc. daily 1600 cc.	-	neg..3cc. +.4cc.	neg.	10	0001210000	-	-
4/19/19 -5/17/19	III Intra-spinal	-	-	-	-	-	neg..3.4cc. neg..3.4cc. neg..3.4cc.	pos. neg. pos.	4 3 4	-	-	0 1/8 1/6

This patient received 18 intravenous injections of arsenobenzol (3 of which were intraspinal); 36 injections of mercury succinimid;150, 4 gm. single and 74 double rubs or a total of 308; 77,000 gr. of potassium iodid by mouth and rectum; 9,800 cc. of sodium iodid solution, equivalent to 980 gm. sodium iodid or 14,700 gr. intravenously, from 12/24/17 to 5/17/19, a period of seventeen months.

Fig. 173.—Treatment chart of a patient subjected to massive treatment with arsphenamine, mercurial inunctions, and the iodids. Note the rapidly unfavorable progress under arsphenamine up to November 20, 1919, and the steady improvement under massive inunctions and huge doses of iodids. The patient is now in excellent health and apparently normal. Infection of nine years' duration.

tors of soil, organism, and treatment may dominate even a favorable combination of the other two.

Is this patient inevitably destined for paresis, and if so, why is he so completely free from all symptoms at this time? Solomon, Fordyce, and others have called attention to a type of case which, while presenting the serology of paresis, none the less lacks its clinical signs. To this type Solomon gives the name *paresis sine paresi*. Is it possible to predict from serologic

findings alone the extent of or outlook for parenchymatous degeneration in given cases? In general, I think not. Therapy and time must be the courts of last resort. There can be no greater mistake than to consign every syphilitic with mental symptoms and every patient with a paretic gold sol curve to limbo.

Is spinal drainage an especially effective method of treating syphilis of the nervous system? In a fairly extended trial I have not been convinced that it accomplishes anything distinctive for the patient.

The possibilities of a really massive therapy in cases presenting an initial unfavorable outlook are well illustrated by Fig. 173

Table 5. CASE 266481

Date	Arsenobenzol	Mercury Succin.	Inunctions	Potassium Iodid	Sodium Iodid	Blood Wassermann	Cerebrospinal fluid Wassermann	Nonne	Cells	Lange	Spinal drain
						4/7/19 neg.					
							4/11/19 +++ .2-.4 c.c.	neg.	232	0,0,0,1,2,2,1,0,0,0	
							4/29/19 +++ .2-.4 c.c.	pos.	107	0,0,0,0,0,0,0,0,0,0	
April 30, 1919 to June 4, 1919	VI	5/6/19 to 5/19/19 VIII				5/29/19 neg.	5/15/19 neg. .2c.c. ++ .4c.c.	neg.	39	0,0,1,2,2,1,0,0,0,0	40 c.c.
							5/28/19 neg. .3-.4 c.c.	neg.	7		55 c.c.

Fig. 174.—Chart of a patient with lues of seven months' duration, whose spinal fluid findings were practically reduced to normal by six intravenous injections of arsphenamine and eight intramuscular injections of mercury succinimid. Spinal drainage was done twice; spinal fluid was normal four months later.

(Case 216746). This chart in particular illustrates a point which the theory of drug-fast spirochetal strains supports, and which I believe my experience exemplifies, namely, that if a patient fails to progress or progresses unfavorably under arsphenamine, an abrupt change to huge inunctions and enormous doses of the iodids given intravenously, by mouth and by rectum, will occasionally accomplish most surprising results. Patients with what seem to be the gravest forms of serologic pathology in the spinal fluid will sometimes respond by serologic cure under as little as six intravenous injections of arsphenamine and eight of mercury succinimid (a soluble salt), intramuscularly—Figs. 174 (Case 266481), 175 (Case 239513), 176 (Case 232210). Others, in

spite of the invoking of the uttermost resort in systemic and intraspinal therapy, will progress to a fatal termination. Between the two there lies a large body of patients in various stages

Table 6. CASE 239513

Date	Arsenobenzol	Mercury Succin.	Inunctions	Potassium iodid	Sodium iodid	Blood Wassermann	Cerebrospinal fluid Wassermann	Nonne	Cells	Lange
July 30, 1918 to Sept. 2, 1918	VI	17				7/25/18 +++	8/4/18 +++.2 c.c. +++ .3 c.c. +++ .4 c.c. +++ .5 c.c.	Pos.	77	0,1,5,4,3,3,1,0,0,0,
						8/24/18 pos.	2/12/19 neg. .3-4 c.c.	neg.	1	
Nov. 1, 1918 to Feb. 11, 1919			50			2/7/19 neg.				
							2/12/19 neg. .3-4 c.c.	neg.	1	

Fig. 175.—Spinal fluid of a supposed taboparesis with neurologic findings of tabes dorsalis. Spinal fluid reduced to normal by six intravenous injections of arsphenamine and seventeen of mercury succinimid intramuscularly. The spinal fluid was still normal six months after the second examination. Interim treatment, fifty inunctions.

of the disease who, in the presence or absence of neurologic findings, present serologic evidence of central nervous system involvement. Systematic investigation of the spinal fluid at

Table 7. CASE 232210

Date	Arsenobenzol	Mercury Succin.	Inunctions	Potassium iodid	Sodium iodid	Blood Wassermann	Cerebrospinal fluid Wassermann	Nonne	Cells	Lange
June 14, 1918 to July 19, 1918	VI	12				5/30/18 +++	5/30/18 +++.2 c.c. +++.3 c.c. +++.4 c.c. +++.5 c.c.	neg.	112	1,2,2,2,3,3,2,0,0,0,0,
						7/13/18 +++				
			40			9/25/18 pos.	9/27/18 neg. 3,.4c.c.	neg.	3	
Oct. 4, 1918 to Nov. 29, 1918	VI					10/18/18 neg. 11/21/18 +++				
July 19, 1918 to April 19, 1919			112			1/21/19 neg. 4/23/19 +++	1/19/19 +.3 c.c.	neg.	6	
May 1, 1919 to May 21, 1919	III						4/23/19 neg. .3-4 c.c.	neg.	2	

Fig. 176.—Patient with tabes dorsalis confirmed by neurologic signs, and tibial periostitis. Spinal fluid reduced to normal by six injections of arsphenamine and fifty-two mercurial inunctions. Such effects as these are not to be regarded as evidence of permanent cure.

every stage of the disease will detect them. Massive and persistent therapy will often reduce to normal what at the outset seemed to be a hopeless picture.

CASE VI (269373)

I want you to have a few moments' relief from the protracted discussion of syphilis, and for that reason I am presenting to you an almost painfully simple case. Mrs. Cohen, as you see, is a patient who appreciates the good things of life, a lady of genial temperament and liberal table habits. The pleasure of living received a sharp setback for Mrs. Cohen about three months ago, at which time she was given a series of three subcutaneous injections of mixed vaccine as a prophylactic against influenza. Since that time she has had repeated attacks of hives and, in fact, of late has not been free from lesions at any time of day or night. Her examination describes her as a seemingly robust Jewish woman, decidedly overweight for her height (5 ft. 5¾ in., 190¼ lbs.), with a well-defined seborrheic dermatitis of the scalp and a seborrhea about the alæ nasi. Scattered over the upper extremities, trunk, and lower extremities are about three dozen pinkish papules, typically urticarial in type. The patient evidently exercises considerable self-control to keep from scratching, and there is accordingly a surprisingly small amount of secondary factitial dermatitis. Most of the teeth have been removed, and those remaining exhibit considerable pyorrhea and are evidently devitalized. A radiogram of the teeth showed three to be apically infected. The tonsils are moderately enlarged, but not grossly septic. The internist's examination of this patient unearthed a history of attacks of right upper abdominal pain suggesting gall-stones, but "not ringing true." The patient has sustained a pelvic operation with the nature of which she is not exactly acquainted, but which apparently caused the cessation of menstruation within a year and was accompanied by a still further increase in weight.

We have then before us a patient who believes her persistent urticaria to be due to prophylactic injections of influenza vaccine. It is a first principle in the examination of any acute dermatosis to endeavor to separate the causal factors into two groups. The elements of these two groups can be isolated by careful general examination and searching inquiry into the history. Briefly aligned, the factors of possible etiologic significance

in this case may be enumerated as follows, although not necessarily in the order of their importance:

Predisposing Causes.—1. Overweight; the patient has gained from 117 at marriage to 200 pounds at the onset of her dermatosis.

2. Overeating.

3. A diet markedly overbalanced in the direction of carbohydrate intake.

4. Race. In my experience Jews are distinctly predisposed to so-called neurotic and vasomotor types of dermatoses.

5. Focal infection—teeth.

6. Endocrine factor? The ovaries have been removed.

7. An inherited unstable mechanism—a sister, for example, developed asthma following pneumonia.

Exciting Cause.—Foreign protein—vaccine by subcutaneous injection.

Cases of this type are not to be confounded with lifelong idiosyncrasies for proteins. The instrumentality of the vaccine I believe in this case to be fortuitous. It is conceivable that some other more trivial exciting cause might have served as a pull on the trigger to discharge this load of predisposing causes. With abundant opportunity to watch the effects of prophylactic injection against influenza I have seen large numbers of patients who, lacking the predisposing causes, have not found vaccine an exciting cause. There can be no escaping the fact, however, that in isolated instances prophylactic vaccination against influenza has served as the exciting cause of eczematoid dermatitis and urticaria. The vaccine and, indeed, the influenzal infection itself unquestionably alter the reactivity of the skin, and in all probability of all tissues of the body to internal and external sources of irritation. This patient's urticaria, then, is to be treated not by lamenting the exciting cause which is now beyond reach, or by a mere resort to antipruritics, but by systematically eradicating the predisposing causes which are responsible for the existence of the process. Critical comment on one or two of the predisposing causes is of interest.

In many men and women passing forty we see the develop-

ment of a cutaneous syndrome the hypothetic basis of which is the excess of intake over elimination. Examination of these patients not infrequently discloses the beginnings of nephritis or a hypertension. The hypersensitiveness of their skins, which leads to the development of dermatitis and urticaria, is not the direct result perhaps of imperfect elimination, but of an indirect lowering of the resistance of the skin to the trauma, irritation, and infection to which it is continually subjected.

Excessive ingestion of carbohydrates has been shown by clinical experience to underlie a variety of inflammatory dermatoses. Excessive ingestion of carbohydrates leads to a hyperglycemia and a slight but definite acidosis. The administration of alkali has long been recognized empirically as good therapy. It is not improbable that patients with chronic urticaria who have had astonishing recoveries under the administration of calcium salts have done so because of the effect of the calcium on the alkali reserve. To obtain an unprejudiced history of excess carbohydrate intake ask the patient to list for you her ordinary breakfast, dinner, and supper. From her own unprejudiced account of her likes and dislikes the etiologic rôle of excess carbohydrate intake will usually stand out conspicuously. Particularly in acne vulgaris and rosacea, extensive seborrheic dermititis, and in many cases of urticaria and eczematoid dermatitis I have known the correction of the diet alone along the lines suggested to be responsible for the complete disappearance of the dermatitis without the use of local measures.

This is scarcely the place to enter into a discussion of the extent of the influence of focal infection in dermatoses. Much controversy, I believe, would be laid to rest if the predisposing rather than exciting rôle of such infections were better appreciated. In a dermatosis such as erythema multiforme or erythema nodosum the relation may be direct, as exemplified in the studies of Rosenow on erythema nodosum. On the other hand, in an exfoliative dermatitis, in chronic eczema, in tuberculids, in chronic urticaria, in rosacea, the relation may be less apparent but none the less real. The failure of a patient to recover on the extraction of infected teeth alone is no more evidence that

focal infection is non-operative than is his recovery under a vaccine made from an infected tooth pulp. Extraction in the one fails to cure because only one of many predisposing causes may have been removed. The vaccine may succeed in the other because it is a well-known fact, to which Engman has called attention, that certain inflammatory dermatoses will yield to the injection of a foreign protein which can have no possible relation to the cause of the disturbance.

CASE VII (207833)

Ten months ago this little youngster entered this same room shielding her eyes with her forearm. The outstanding fact of her history is that two weeks before she was brought to the clinic she developed influenza. While she made a prompt recovery from the constitutional symptoms, some trouble with her eyes made its appearance before she was up and around. It was noticed that she could not bear the light, that the eyes were becoming increasingly red, and that there was a constant flow of tears. A year ago she had accompanied her mother to the clinic and both she and her mother were found to have positive Wassermann tests on the blood. Circumstances had made it impossible to give the child arsphenamine at that time, but she had been placed on inunctions, and up to the time of her attack of influenza she had taken 160 gm. of unguentum hydrargyri. The child's examination reports her as a well-built, fairly well-developed little girl somewhat below the normal in size. Dermatologically, there is nothing to suggest a syphilitic infection. There is, however a slight anterior bowing of the tibiæ and definite Graves' scapulæ. About the angles of the mouth there is a fine radiating, extremely superficial linear scarring. Only the incisors are second dentition teeth and the upper centrals do not show definite Hutchinsonian characteristics. Now that the photophobia has disappeared, I should like to have you get by inspection of the full face the peculiar "hunch" or intuitive impression of the facies of lues hereditaria. This "hunch" does not consist of an enumeration of details, such as the flattened nasal bridge, the slight upward and outward flare of the nostrils, the

full dome-like forehead with its prominent frontal bosses. If these characteristics are well marked the impression is, of course, obvious and striking. The recognition of the subtler changes, however, seems to me to depend on a peculiar expression of sleepiness and unalertness, a "washed-out" look in the upper half of the face present even in patients whose corneæ have not been obscured by interstitial keratitis. The primary stigmata which this child presents are not well marked. The mere notching of teeth is not of special significance. A total absence of upper central incisors in the second dentition would, to my mind, be quite as significant of heredosyphilis as would the most characteristic screwdriver-shaped, anteroposteriorly thickened tooth. The scaphoid scapulæ are rather nutritional subnormalities than definite stigmata. The anterior bowing of the tibiæ in these cases is not due primarily to periostitis, but rather to the tendency to congenital osseous hyperplasia which uterine syphilis presents. A positive Wassermann is not necessary in the identification of this type of syphilis and is often not obtained. In a series of cases under my observation only 42 per cent. had strongly positive Wassermanns on first examination. It is by no means uncommon in lues hereditaria as in late acquired syphilis to have the gravest accidents occur in patients whose syphilis cannot be confirmed by a positive Wassermann.

The ophthalmologic examination of this patient at the time of the acute attack showed the typical changes of early interstitial keratitis. The onset of this complication illustrates again the delicate balance between the forces tending to step up and drag down the resistance of a given patient. During the past year we have seen some very striking examples of the ill effect of influenzal infection upon this resistance. This patient was under moderately intensive treatment with mercury at the time of the onset of her complication. A drop in resistance produced by the intercurrent infection resulted in a fulminating outbreak of interstitial keratitis. A similar complication may follow the reduction in resistance and the changes in the defensive mechanism of the body that occur in other acute infections and in pregnancy. The onset of interstitial keratitis during the administration of

mercury leads one to speculate on the adequacy of this drug in the therapy of syphilis. We know that its spirocheticidal value in the body is low. Condylomas loaded with *Spirochæta pallida* and mucous patches in the mouth and throat can appear in the midst of a so-called intensive course of inunctions or insoluble intramuscular injections. Grave forms of neurologic recurrences are well known to occur in spite of the most intensive use of mercury. In view of these considerations it hardly seems wise to make it a sole reliance in the treatment of any phase of syphilis. Yet occasionally a curious hesitation about the use of arsphenamine is encountered among those especially concerned with the treatment of hereditary syphilis. Some of this is undoubtedly due to the technical difficulties in the administration of the drug to children. Personally, I believe that much more rapid results will be secured, and much secondary damage to eyesight prevented, when arsphenamine is employed in treating interstitial keratitis with an intensity at least equal to that which has become conventional in adults. This child would have received arsphenamine following her first examination had it been possible. In five weeks, under six injections of 2 to 3 dg. of novarsenobenzol, the process whose fulminating onset threatened disastrous impairment of sight was almost completely arrested. Ten months after the onset of the trouble, the patient having received a second course of intravenous injections, is again in school. The residual damage to the cornea is almost nil.

CASE VIII (258301)

It is not my intention to show this patient because of his ophthalmoplegia. He has a late tabes dorsalis, and at the time of his first examination had a spinal fluid with the following findings: Wassermann positive, Nonne positive, 87 lymphocytes, gold sol 0023320000. At the conclusion of four months' routine therapy without the employment of intraspinal measures the spinal fluid findings were Wassermann negative, Nonne negative, 2 lymphocytes. The treatment of this patient presented special difficulties which are frequently met with in the types of cases I am called upon to handle. So frequently do I

encounter the urgent need for intensive therapy and the physical make-up that cannot stand hammering that I have expressed myself as believing that the cure or arrest of syphilis depends in an almost literal sense on the patient's kidneys. If the kidneys will stand the hammering, the number of cases of syphilis which cannot be cured or permanently arrested will be reduced to a comparatively small group of parenchymatous degenerations in the nervous system and visceral, particularly cardiovascular accidents, in which a large part of the damage has been done long before adequate treatment is instituted. Believing as I do about this matter, I have made it my business to try to devise methods for the protection of the kidney against the renotropic effects of arsenic and of mercury. A conviction that the insoluble mercurial salts, such as the salicylates, do not have a therapeutic value sufficient to compensate for the damage which they inflict on the renal tissues, has led me to abandon them in favor of the soluble salts (succinimid, bichlorid), intramuscularly and inunctions. In the same way I have come to recognize in focal infections, particularly of the teeth and tonsils, a factor predisposing patients to renal reaction under treatment.

This patient, who is sixty-one years of age, presents the familiar combination of a crying need for intensive therapy, and a renal mechanism so irritable that unless some means can be found to protect it and to diminish its irritability, all prospect of arresting the cerebrospinal process is at an end. Before the institution of treatment the patient's urine was practically normal. He was given four successive injections of mercury succinimid ($\frac{1}{6}$ gr.) daily. This dosage and the interval is usually well tolerated even by elderly patients in our experience. Signs of renal reaction may not appear until arsphenamine is combined with the mercury, or the mercurial course is nearly finished. In this patient the four injections above mentioned resulted in a fulminating nephritis. His general examination had disclosed the presence of a number of devitalized and infected teeth. I hesitated, however, for the psychologic effect to advise wholesale extractions at the first sitting. Following the first urine examination after treatment was begun, the patient, a decidedly sick

man by that time, was put to bed. The urine was found to be loaded with casts. It contained a moderate amount of albumin

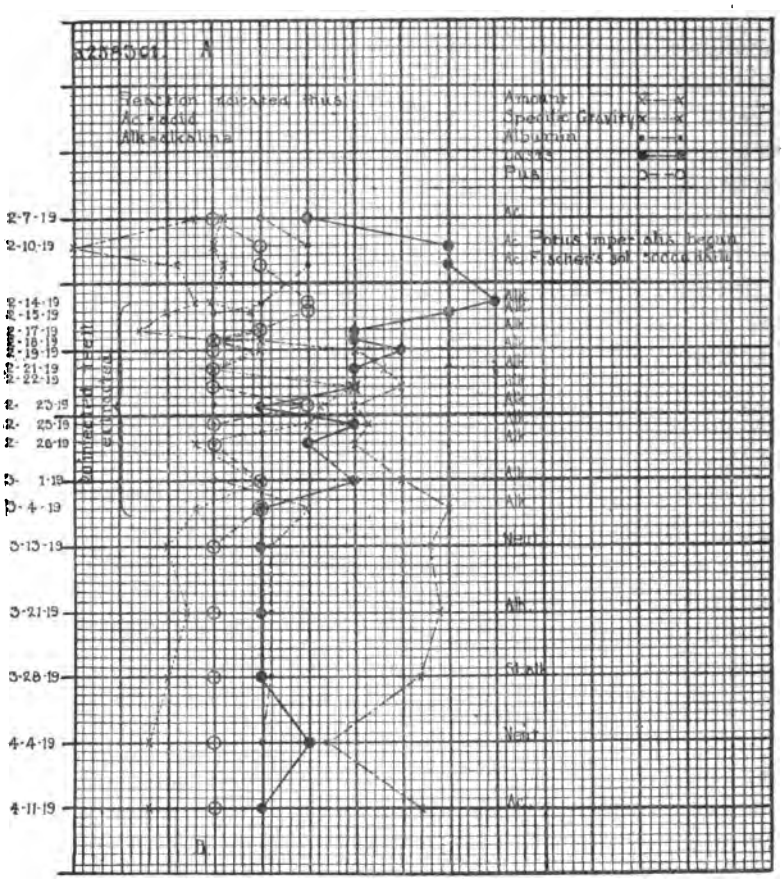


Fig. 177.—Chart illustrating the response of a renal treatment reaction to alkali therapy and the removal of foci of infection (teeth). The line *A–B* represents the normal line of average urinary findings. The condition of the urine on February 15, 1919, represents an extremely severe nephritis. The rapid subsidence of the process under the measures instituted is apparent. Recent examination of the patient shows normal urine, normal kidney function, and normal blood urea.

and a trace of blood. Following the practice suggested by experimental studies of mercurial poisoning, it is my custom systematically to alkalinize all patients showing any signs of reaction

to intensive mercurial treatment by the use of *potus imperialis* by mouth, and, when indicated, the administration of Fischer's solution by rectum. This therapy undoubtedly had an influence in reducing to order this patient's refractory kidneys, but the most striking effect both on his kidneys and constitutional condition became apparent when the extraction of the infected teeth was begun. In the course of fourteen days, twenty snags, stumps, and apically infected teeth were removed. The renal response is illustrated in Fig. 177. The transformation in the patient himself was fully as striking. While the first conspicuous drop in the cast content of the urine followed the instituting of alkali therapy and low protein, salt-free diet, the final reduction was the sequel of the extractions.

Critically speaking, undoubtedly much of the immediate good effect must be attributed to hospitalization and the vigorous application of alkali therapy and diet. The ability of the patient to tolerate further treatment is, however, the real test of the effectiveness of our management. March 13th, one month and six days after the onset of the patient's nephritis, his treatment was resumed and he received a series of ascending doses of neo-arsphenamine with somewhat less than the usual amount of renal irritation we expect in patients of his age. Subsequent study of his case has shown that while the removal of his focal infections has greatly reduced his renal irritability, he still has less than the normal tolerance of mercury and is unable to take this drug in combination with arsphenamine. That his tolerance of intensive therapy was greatly increased by proper attention to the teeth seems undoubted. Duke, of Kansas City, has called attention to the favorable effect of the extirpation of foci on the general course of the syphilitic infection as such, an observation which our experience confirms. If the general course of the infection can be favorably modified by the extirpation of focal infections, and the patient's tolerance of treatment can be increased by the same means, a double reason is apparent why every syphilitic, *as a preliminary to his therapy*, should be thoroughly examined and treated for his focal infections.